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James W. Kalat

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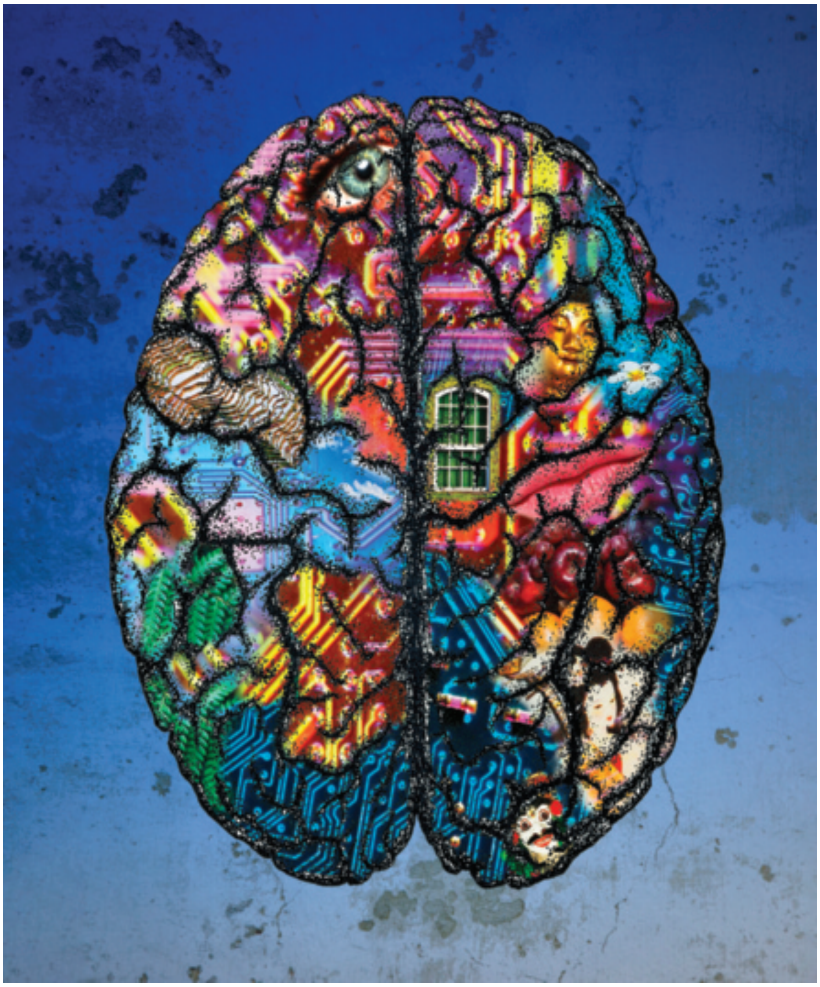

Biological Psychology

14th Edition

James W. Kalat

North Carolina State University

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About the Author

James W. Kalat (rhymes with ballot) is professor emeritus of psychology at North Carolina State University, where he taught courses in introduction to psychology and biological psychology from 1977 through 2012. Born in 1946, he received a BA *summa cum laude* from Duke University in 1968, and a PhD in psychology from the University of Pennsylvania in 1971. He is also the author of *Introduction to Psychology* (12th edition) and co-author with Michelle Shiota of *Emotion* (3rd edition). In addition to textbooks, he has written journal articles on taste-aversion learning, the teaching of psychology, and other topics. He was twice the program chair for the annual convention of the American Psychological Society, now named the Association for Psychological Science. A remarried widower, he has three children, two stepsons, and five grandchildren.

To Ken King, my first editor and since then long-time friend, whose confidence in me almost half a century ago led to these fourteen editions.

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Preface

Biological psychology is the most interesting topic in the world. No doubt people in other fields think their topic is the most interesting, but they are wrong. This really is the most interesting. Most people laugh when I say that, but fellow specialists in this field just nod their heads in agreement, "Yes, that's right." I don't mean that memorizing brain anatomy or learning the names of neurotransmitters is more interesting than other facts. What I mean is that biological psychology deals with questions that should be of extreme interest to anyone who cares about theoretical issues. In a universe composed of matter and energy, why is there such a thing as conscious experience? What does it mean to say that your brain activity and your mental activity are the same thing?

Research is intensive in biological psychology and related fields. In 2021, the journal *Behavioral Neuroscience* published 803 pages, *Nature Neuroscience* published 1780 pages, the *Journal of Cognitive Neuroscience* another 2588 pages, *Neuron* 4108 pages, and *Neuroscience* a whopping 6188 pages. Those are just a few of the primary journals in this field, and much of the best research is published in more general journals such as *Science and Nature*. I have done my best to identify the most important points that I think will interest the readers of this book, but inevitably any book that is intended to be "complete" would be impossibly long.

Each chapter is divided into modules that begin with an introduction and learning objectives and end with a summary, a list of key terms, and review questions. This organization enables instructors to assign part of a chapter per day instead of a whole chapter per week. Modules can also be covered in a different order, or of course omitted.

I assume that readers have a basic background in psychology and biology, and that they understand such terms as *classical conditioning, reinforcement, vertebrate, mammal, gene, chromosome, cell*, and *mitochondrion*. I also assume at least a high school chemistry course. Those with a weak background in chemistry or a fading memory of it may consult Appendix A.

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Changes in this Edition

This edition includes revised content throughout, with many new references, including more than 500 from 2019–2022. Some of the figures are new or revised, and nearly all of the review questions at the end of modules are new. The Table of Contents will look familiar to users of the previous edition, the major exception being that the Introduction has become the first module of Chapter 1. Many changes occur within each chapter, of course.

Here are a few highlights of new content:

- This edition continues the tradition of including photographs and quotes of prominent researchers, now adding Linda Buck, Suzana Herculano-Houzel, Okihide Hikosaka, Tirin Moore, Miguel Nicolelis, Lauren Orefice, Gina Poe, V.S. Ramachandran, and Nora Volkow. Students can name hundreds of singers, actors, and athletes, but I have found that they cannot name any psychologists other than their own faculty, a few dead white males, and "Doctor Phil." I think it is good for them to think of scientists as real people, not that different from themselves, and to become familiar with a few important names.
- Since the first edition, I have dutifully followed all the revisions of the APA publication manual's reference style. The latest APA edition calls for listing up to 20 authors per article, plus a website. That would add a huge number of pages at the back of the book, for little benefit. Instead, I have used the reference style of the journal *Neuron*, which is a modification of the Harvard style.

- The first chapter includes a section on Neuroethics, including issues in dealing with human participants.
- New research highlights the important contributions of gut bacteria and mitochondrial genes, two topics historically overlooked.
- People who are blind localize sounds more accurately than previously documented. Previous studies measured sound localization by asking people to point, but people who are blind are not experienced at pointing.
- A new explanation has emerged for why older people have trouble understanding voices in a noisy room. After many auditory receptors have become unresponsive, the auditory cortex adjusts its synapses, in effect "turning up the volume knob" to compensate. That change improves hearing in quiet environments, but in a noisy environment it magnifies the background noises as well as whatever one hopes to hear.
- Several studies have found differences between men and women in the mechanisms of pain. Unfortunately, most research with laboratory animals has focused entirely on male rodents, on the assumption that males are less variable (wrong) and that the mechanisms are the same for males and females (also wrong).
- The taste of water is more than a texture. Water produces a distinctive pattern of response in the receptors for sour taste.
- One reason why L-dopa is more effective for some Parkinson's patients than others is that some people have intestinal bacteria that break down L-dopa.
- Approximately 30% of dreams (more for some people than others) are "white dreams," with less brain activation and no memorable content.
- Many supplements marketed for weight loss or memory improvement include chemicals not listed on the label, sometimes posing health risks. Many of these supplements have doubtful effectiveness.
- A study of prisoners with a history of extreme impulsive violence found that almost half of them had one or more rare genetic variants linked to cognitive processes.
- The hippocampus does not transfer memories to the cortex. Rather, both places store memories in parallel, but the hippocampal stores tend to fade faster.
- According to fMRI data, both hemispheres respond to language up to about age 6, but after that the right hemisphere's response declines, especially for production.
- One difference between the cortex and the cerebellum that might explain why cortical activity is conscious and cerebellar activity is not, is that the cortex has long-range reciprocal connections enabling each area to influence many others and receive feedback from them.
- As people become addicted to a drug, their brains show less dopamine response to the drug itself but increased response to cues for the drug.
- Two new explanations have emerged for why antidepressant drugs increase serotonin levels quickly but take weeks before they relieve depression.
- Several psychedelic drugs have shown promise as fast-acting antidepressants.
- For decades, parents of many autistic children have reported that having a fever causes their child to act more like typical children. We now see why.
- Also, throughout the text, many studies have been deleted because they proved difficult to replicate.

Instructor Ancillaries

***Biological Psychology*, 14th edition,** is accompanied by an array of supplements developed to facilitate both instructors' and students' best experience inside as well as outside the classroom. All of the supplements continuing from the 13th edition have been revised and updated. Cengage invites you to take full advantage of the teaching and learning tools available to you and has prepared the following descriptions of each.

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The author himself wrote the all-new items for the test bank, including multiple-choice, true-false, completion, and short answer. The test bank includes a special file intended for a comprehensive final exam.

Online Instructor's Manual

The manual includes learning objectives, key terms, a detailed chapter outline, a chapter summary, lesson plans, discussion topics, student activities, media tools, a sample syllabus, and an expanded test bank. The learning objectives are correlated with the discussion topics, student activities, and media tools.

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I welcome correspondence from both students and faculty. E-mail: james_kalat@ncsu.edu

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Chapter 1

It is tempting to try to "get inside the mind" of people and other animals, to imagine what they are thinking or feeling. In contrast, biological psychologists try to explain behavior in terms of its physiology, development, evolution, and function.

(Source: C. D. L. Wynne, 2004)

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The Cellular Foundations of Behavior

Chapter Outline

Module 1.1

The Biological Approach to Behavior
Biological Explanations of Behavior
Career Opportunities
Neuroethics
In Closing: Your Brain and Your Experience

Module 1.2

Neurons and Other Cells
Neurons
Glia
The Blood–Brain Barrier
Nourishment of Vertebrate Neurons
Other Cells: The Gut Bacteria
In Closing: The Cells

Module 1.3

The Action Potential
The Resting Potential of the Neuron
The Action Potential
Propagation of the Action Potential
The Myelin Sheath and Saltatory Conduction
Local Neurons
In Closing: Neurons and Messages

Learning Objectives

After studying this chapter, you should be able to:

1. State the mind–brain problem and contrast monism with dualism.
2. List three points that are important to remember from this text.
3. Give examples of physiological, ontogenetic, evolutionary, and functional explanations of behavior.
4. Discuss the ethical issues of research with laboratory animals.
5. Describe neurons and glia, the cells that constitute the nervous system.
6. Contrast axons with dendrites.
7. Summarize how the blood–brain barrier relates to protection and nutrition of neurons.
8. State the chemicals necessary for the brain's nutrition.
9. Describe the importance of the bacteria in the intestines.
10. Contrast action potentials with electrical transmission.
11. Explain what causes the resting potential of a neuron.
12. Discuss how the movement of sodium and potassium ions produces the action potential and recovery after it.
13. State the all-or-none law of the action potential.
14. Explain how the action potential propagates along the axon.
15. Describe the importance of the refractory period, the myelin sheath, and local neurons.

It is often said that Man is unique among animals. It is worth looking at this term *unique* before we discuss our subject proper. The word may in this context have two slightly different meanings. It may mean: Man is strikingly different—he is not identical with any animal. This is of course true. It is true also of all other animals: Each species, even each individual is unique in this sense. But the term is also often used in a more absolute sense: Man is so different, so "essentially different" (whatever that means) that the gap between him and animals cannot possibly be bridged—he is something altogether new. Used in this absolute sense the term is scientifically meaningless. Its use also reveals and may reinforce conceit, and it leads to complacency and defeatism because it assumes that it will be futile even to search for animal roots. It is prejudging the issue.

Niko Tinbergen (1973, p. 161)

Module 1.1

The Biological Approach to Behavior

Learning Objectives

After studying this chapter, you should be able to:

1. State the mind–brain problem and contrast monism with dualism.
2. List three points that are important to remember from this text.
3. Give examples of physiological, ontogenetic, evolutionary, and functional explanations of behavior.
4. Discuss the ethical issues of research with laboratory animals.

Of all the questions that people ask, two stand out as the most profound. One of those questions deals with physics. The other pertains to the relationship between physics and psychology.

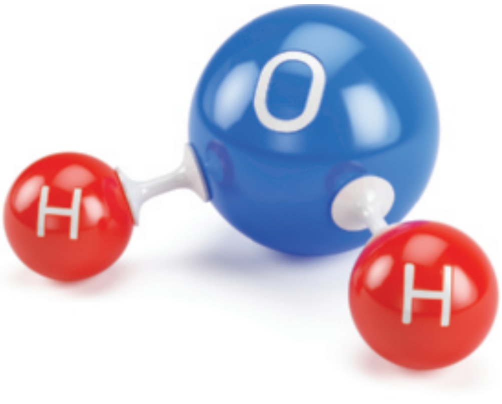
Gottfried Leibniz (1714) posed the first of these questions: "Why is there something rather than nothing?" It would seem that nothingness would be the default state. Evidently, the universe—or whoever or whatever created the universe—had to be self-created.

So . . . how did that happen?

Furthermore, given the existence of a universe, why this particular type of universe? As Steven Vigdor (2018, p. 1) noted, "Our universe is habitable. It did not have to be so." The Big Bang that started the universe contained an as-yet unexplained asymmetry that caused the development of more matter than antimatter. If matter and antimatter had been equal, there could be no stars, planets, or anything else. Our universe has protons, neutrons, and electrons with particular dimensions of mass and charge. It has four fundamental forces: gravity, electromagnetism, the strong nuclear force, and the weak nuclear force. Those properties and dimensions have values that seem arbitrary, but if they had been much different, stars and planets could not have developed, or if they had developed, they would not have lasted long enough for life to evolve. Life could have evolved in a slightly different universe—and, who knows, maybe some universes could have been even better (Adams, 2019)—but many aspects of the universe had to be almost exactly what they are. One item that had to be narrowly constrained is the structure of a water molecule. In a water molecule, the two hydrogen ions form a 104.5° angle (Figure 1.1). Because of that angle, one end of the water molecule has a slight positive charge and the other has a slight negative charge. The charge difference enables water molecules to attract one another electrically by just the right amount. If water molecules attracted one another a bit less, all water would be a gas (steam). If the molecules attracted one another a bit more strongly, water would always be a solid (ice).

Figure 1.1 A water molecule

Because of the hydrogen-oxygen-hydrogen angle, one end of a water molecule is more positive and the other negative. The exact difference in charge causes water molecules to attract one another just enough to be a liquid.



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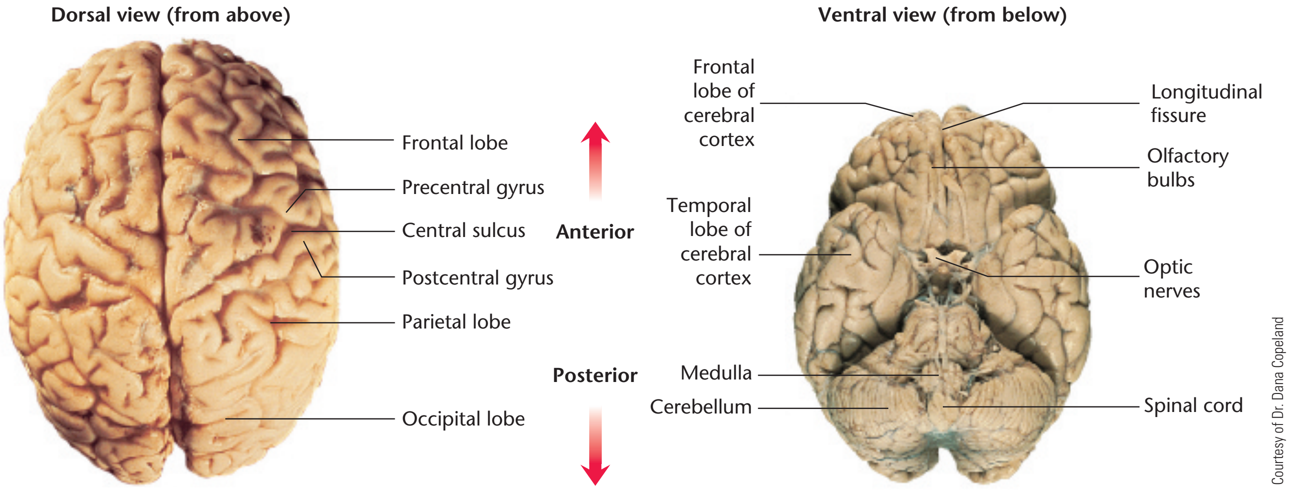
Why is the universe suitable for sustaining life? Maybe it's just a coincidence. (Lucky for us, huh?) Or maybe intelligence of some sort guided the formation of the universe. That hypothesis clearly goes beyond the reach of empirical science. Another possibility is that other universes exist, and we know about only the one in which life like ours could evolve. Physicists have persuasive theoretical reasons for supposing other universes, but that idea also goes beyond the reach of empirical science.

I said that two question stand out as the most profound. The second one is this: In a universe composed of matter and energy, why is there such a thing as consciousness? In our universe, consciousness exists. It did not have to be so. Computers can perform increasingly intelligent operations, presumably without being conscious, but when we perform the same operations, conscious experience accompanies them. Why? The **mind–brain problem** or the **mind–body problem** is the question of how and why certain types of brain activity are conscious. We shall deal with this question in more detail in a later chapter.

Figure 1.2 Two views of the human brain

The brain has an enormous number of divisions and subareas; the labels point to a few of the main ones on the surface of the brain.



Courtesy of Dr. Dana Copeland

The Field of Biological Psychology

In a sense, all psychology is biological. You are a biological organism, and everything that you do is part of your biology. However, it is helpful to distinguish among levels of explanation. Some aspects of psychology are best described in terms of cultural, social, and cognitive influences, while others require reference to genetics, evolution, hormones, body physiology, and brain mechanisms.

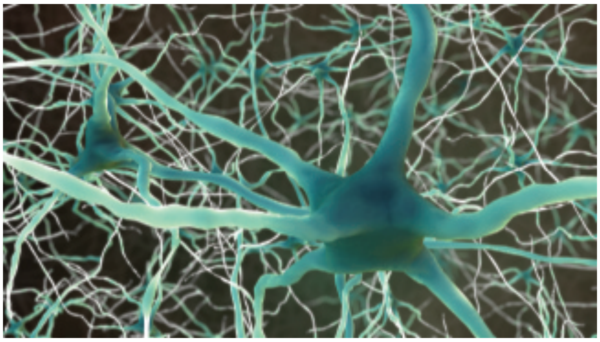
Biological psychology is the study of the physiological, evolutionary, and developmental mechanisms of behavior and experience. It is approximately synonymous with the terms *biopsychology*, *psychobiology*, *physiological psychology*, and *behavioral neuroscience.* The term *biological psychology* emphasizes that the goal is to relate biology to issues of psychology. *Neuroscience* includes much that is relevant to behavior, but it includes more detail about anatomy and chemistry.

Biological psychology is not only a field of study but also a point of view. It holds that we think and act as we do because of brain mechanisms, and that we evolved those brain mechanisms because ancient animals built this way survived and reproduced.

Biological psychology deals with brain activity. Figure 1.2 offers a view of the human brain from the top (what anatomists call a *dorsal* view) and from the bottom (a *ventral* view). The labels point to a few important areas that will become more familiar as you proceed through this text. An inspection of a brain reveals distinct subareas. At the microscopic level, we find two kinds of cells: the *neurons* (Figure 1.3) and the *glia.* Neurons, which convey messages to one another and to muscles and glands, vary enormously in size, shape, and functions. The glia, generally smaller than neurons, have many functions but they do not convey information over great distances. The activities of neurons and glia somehow produce an enormous wealth of behavior and experience. This book is about researchers' attempts to elaborate on that word *somehow.*

Figure 1.3 Neurons, magnified

The brain is composed of individual cells called neurons and glia.



Nathan Devery/Science Source

Three Main Points to Remember

This book presents a great deal of factual information. Regardless of how many details you learn or forget, at least three general points should stick with you forever:

1. Perception occurs in your brain. When something contacts your hand, the hand sends a message to your brain. You feel it in your brain, not your hand. Electrical stimulation of your brain could produce a hand experience even if you had no hand. A hand disconnected from your brain has no experience. Similarly, when you see something, the experience is in your head, not "out there." You do *not* send "sight rays" out of your eyes, and even if you did, they wouldn't do you any good. The chapter on vision elaborates on this point. Furthermore,

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what you perceive is not what something actually *is*. Colors are what the light rays cause your brain to do, and sounds are what air waves cause your brain to do. Light waves are not colors and air waves are not sounds.

2. Mental activity and certain types of brain activity are, so far as we can tell, inseparable. This position is known as **monism**, the idea that the universe consists of only one type of being. (The opposite is **dualism**, the idea that minds are one type of substance and matter is another.) Nearly all neuroscientists and philosophers support some version of monism.

   It is not easy to get used to the concept of monism. People sometimes ask whether brain activity causes thoughts, or whether thoughts direct the brain activity (e.g., Miller, 2010). According to monism, that question is like asking whether temperature controls the movement of molecules, or whether the movement of molecules causes temperature. Neither one causes the other. They are just different ways of describing the same thing.
3. People differ from one another in countless ways, and many of the differences can be traced to differences in the brain. Close your eyes and imagine the Eiffel Tower. Do you suppose that other people have nearly the same experience when they picture it "in their mind's eye"? Nope. Some people have an experience almost as clear and detailed as actually seeing something, and others have no visual experience at all. People vary in how well they recognize faces. They differ in their sensitivity to tastes, smells, and pain. They differ in their ability to understand voices in a noisy environment, and in their ability to recall personal experiences. They differ in how much sleep they need per night. The list goes on, and the behavioral differences are rooted in brain differences.

Biological Explanations of Behavior

Commonsense explanations of behavior often refer to intentional goals such as, "He did this because he was trying to . . ." or "She did that because she wanted to . . ." But often, we have no reason to assume intentions. A 4-month-old bird migrating south for the first time presumably does not know why. The next spring, when she lays an egg, sits on it, and defends it from predators, she doesn't know why. Even humans don't always know the reasons for their own behaviors. Yawning and laughter are two examples. You do them, but can you explain what they accomplish? Even when an intention is clear—for example, you are buying a sandwich because you plan to eat it—the intention does not explain anything. Something else, after all, caused the intention.

In contrast to commonsense explanations, biological explanations of behavior fall into four categories: physiological, ontogenetic, evolutionary, and functional (Tinbergen, 1951). A **physiological explanation** relates a behavior to the activity of the brain and other organs. It deals with the machinery of the body, for example, the chemical reactions that enable hormones to influence brain activity and the routes by which brain activity controls muscle contractions.

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Researchers continue to debate the function of yawning. Brain mechanisms produce many behaviors without our necessarily knowing why.

The term *ontogenetic* comes from Greek roots meaning the origin (or genesis) of being. An **ontogenetic explanation** describes how something develops. For example, if we want to explain why males and females differ on average in some regard, we might examine behavior at various ages and relate it to changes in the nervous system.

An **evolutionary explanation** reconstructs the evolutionary history of a structure or behavior. The characteristic features of an animal are almost always modifications of something found in ancestral species. For example, bat wings are modified arms, and porcupine quills are modified hairs. In behavior, monkeys use tools occasionally, and humans evolved elaborations on those abilities that enable us to use tools even better (Peeters et al., 2009). Evolutionary explanations call attention to behavioral similarities among related species.

A **functional explanation** describes *why* a structure or behavior evolved as it did. Within a small, isolated population, a gene can spread by accident through a process called *genetic drift*. For example, a dominant male with many offspring spreads all his genes, including some that may have been irrelevant or even disadvantageous. However, a gene that is prevalent throughout a species probably provided some advantage—at least in the past, though not necessarily today. A functional explanation identifies that

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Steve Maslowski/Science Source

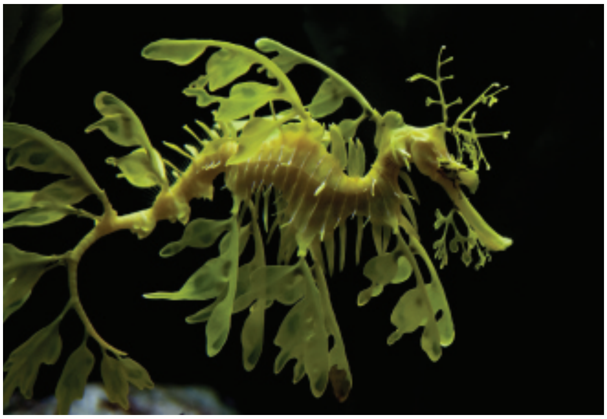
Unlike other birds, doves and pigeons can drink with their heads down. Others fill their mouths and then raise their heads. A physiological explanation would describe these birds' nerves and throat muscles. An evolutionary explanation states that all doves and pigeons share this behavioral capacity because they inherited their genes from a common ancestor.

advantage. For example, many species have an appearance that matches their background (Figure 1.4). A functional explanation is that camouflaged appearance makes the animal inconspicuous to predators. Some species use their behavior as part of the camouflage, such as fish that live among kelp, look like kelp, and act like kelp.

To illustrate two types of biological explanations, consider the example of how certain moth species react to sound. For sound waves that humans hear, up to about 20,000 Hz (hertz, or cycles per second), the moths do not react at all. For waves at 20,000 to 100,000 Hz, which we regard as ultrasonic, a moth turns and flies away from the sound source. If the sound gets louder, the moth either dives for the ground or flies erratically. The physiological explanation starts with the moth's ears, which are sensitive only to sound waves at 20,000 to 100,000 Hz. When the sound is louder in one ear than in the other, it triggers a reflex that turns the moth until the two ears respond equally, enabling the moth to fly away. At a certain level of loudness, the ears respond equally and at maximum, no matter where the moth turns. At that point, connections in the moth's head stimulate either a dive or helter-skelter flight (Roeder, 1967).

Figure 1.4 A seadragon, an Australian fish related to the seahorse, lives among kelp plants, looks like kelp, and usually drifts slowly, acting like kelp.

A functional explanation is that potential predators overlook a fish that resembles inedible plants. An evolutionary explanation is that genetic modifications expanded smaller appendages that were present in these fish's ancestors.



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A functional explanation deals with why the moth's hearing system evolved this way. Moths in flight are vulnerable to attack by bats that find moths by emitting calls at 20,000 to 100,000 Hz and listening for echoes. As soon as a moth hears *anything*, it treats it as danger. By turning until the ears are equally stimulated, it can fly away from the bat. A moth can hear bat calls when the bat is too far away to hear the echo. If the bat gets close enough to hear an echo, that is the distance at which the bat's calls will be so loud to the moth that both ears reach maximum response. At that point, flying away is no longer a good strategy, because bats are faster. Diving for the ground or flying helter-skelter might work. Probably not, but worth a try. The moths evolved a simple hearing system that increases their chance for survival.

Just for fun, here is something you can try yourself: When you observe moths clustering around your house light at night, jingle some keys. If you manage to produce some high-frequency sound waves, the moths will react strongly. You managed to drive the moths "batty."

Try It Yourself

To further illustrate the four types of biological explanation, consider how they all apply to another example, birdsong (Catchpole and Slater, 1995):

Type of Explanation	**Example from Birdsong**
Physiological	A particular area of a songbird brain grows under the influence of testosterone; hence, it is larger in breeding males than in females or immature birds. That brain area enables a mature male to sing.
Ontogenetic	In certain species, a young male bird learns its song by listening to adult males. Development of the song requires certain genes and the opportunity to hear the appropriate song during a sensitive period early in life.
Evolutionary	Certain pairs of species have similar calls. For example, dunlins and Baird's sandpipers, two shorebird species, give their calls in distinct pulses, unlike other shorebirds. The similarity suggests that the two evolved from a single ancestor.

Functional	In many bird species, only the male sings. He sings only during the reproductive season and only in his territory. The functions of the song are to attract females and warn away other males.

Stop & Check

1. How does an evolutionary explanation differ from a functional explanation?

See page 13 for the answer.

Career Opportunities

If you want to consider a career related to biological psychology, you have a range of options relating to research and therapy. Table 1.1 describes some of the major fields.

A research position ordinarily requires a PhD degree. People with a master's or bachelor's degree might work in a research laboratory, but they would not direct it. Many people with a PhD hold college or university positions, where they perform some combination of teaching and research. Others have pure research positions in laboratories sponsored by the government, drug companies, or other industries.

Table 1.1 | Fields of Specialization

Specialization	Description
Research Fields	**Research positions ordinarily require a PhD. Researchers are employed by universities, hospitals, pharmaceutical firms, and research institutes.**
Neuroscientist	Studies any aspect of the nervous system. (This term includes the next five, as well as others not listed.)
Behavioral neuroscientist (almost synonyms: psychobiologist, biopsychologist, or physiological psychologist)	Investigates how the brain and other organs influence behavior.
Cognitive neuroscientist	Uses brain research, such as scans of brain anatomy or activity, to analyze and explore people's knowledge, thinking, and problem solving.
Neuropsychologist	Conducts tests to determine the abilities and disabilities of people with brain damage or impairment. Most neuropsychologists have both psychological and medical training.
Psychophysiologist	Measures heart rate, breathing rate, brain waves, and other body processes.
Neurochemist	Investigates the chemical reactions in the brain.
Comparative psychologist (almost synonyms: ethologist, animal behaviorist)	Compares the behaviors of different species and relates their behaviors to their ancestry and their ways of life.
Evolutionary psychologist (almost synonym: sociobiologist)	Relates behaviors, especially social behaviors, to the functions they have served and, therefore, the presumed selective pressures that caused them to evolve.
Practitioner Fields of Psychology	**Require a PhD, PsyD, or master's degree. Practitioners often need to understand neuroscience at least well enough to communicate with a client's physician. They work in hospitals, clinics, schools, colleges, and private practice.**
Clinical psychologist	Helps people with emotional, cognitive, or behavioral problems.
Counseling psychologist	Helps people make educational, vocational, and other decisions.
School psychologist	Identifies educational needs of schoolchildren, devises a plan to meet the needs, and then helps teachers implement it.
Medical Fields	**Require an MD plus about four years of additional study and practice in a specialization. Physicians are employed by hospitals, clinics, medical schools, and in private practice. Some conduct research in addition to treating patients.**
Neurologist	Treats people with brain damage or diseases of the brain.
Neurosurgeon	Performs brain surgery.
Psychiatrist	Helps people with emotional distress or troublesome behaviors, often using drugs or other medical procedures.
Allied Medical Field	**Ordinarily require a master's degree or more. Practitioners are employed by hospitals, clinics, private practice, and medical schools.**
Physical therapist	Provides exercise and other treatments to help people with muscle or nervous system problems that impair movement.
Occupational therapist	Helps people improve their ability to perform functions of daily life, for example, after a stroke.
Social worker	Helps people deal with personal and family problems. The activities of a social worker overlap those of a clinical psychologist.

Fields of therapy include clinical psychology, counseling psychology, school psychology, medicine, and allied medical practice such as physical therapy. These fields range from neurologists (who deal exclusively with brain disorders) to social workers and clinical psychologists, who need to recognize possible signs of brain disorder so they can refer a client to a proper specialist.

Anyone who pursues a career in research needs to stay up to date on new developments by attending conventions, consulting with colleagues, and reading research journals, such as *Neuron*, *Journal of Neuroscience*, *Neurology*, *Behavioral Neuroscience*, *Brain Research*, *Nature Neuroscience*, *Journal of Cognitive Neuroscience*, and *Archives of General Psychiatry.* But what if you are entering a field on the outskirts of neuroscience, such as clinical psychology, school psychology, social work, or physical therapy? In that case, you want to stay current on major developments, at least enough to converse intelligently with medical colleagues. You can find much information in magazines such as *American Scientist* or *Scientific American Mind* or at websites such as the Dana Foundation at www.dana.org.

Neuroethics

Research in biological psychology and related fields attempts to understand and sometimes modify behavior. Difficult ethical issues arise.

Issues Concerning Animal Research

Several ethical disputes resist agreement. Among those issues are abortion and the use of animals in research. In both cases, well-meaning people on each side of the issue insist that their position is proper and ethical. The dispute is not between good people and bad people. It is between two views of what is good.

Given that most biological psychologists and neuroscientists are primarily interested in the human brain and human behavior, why do they study nonhumans? Here are four reasons:

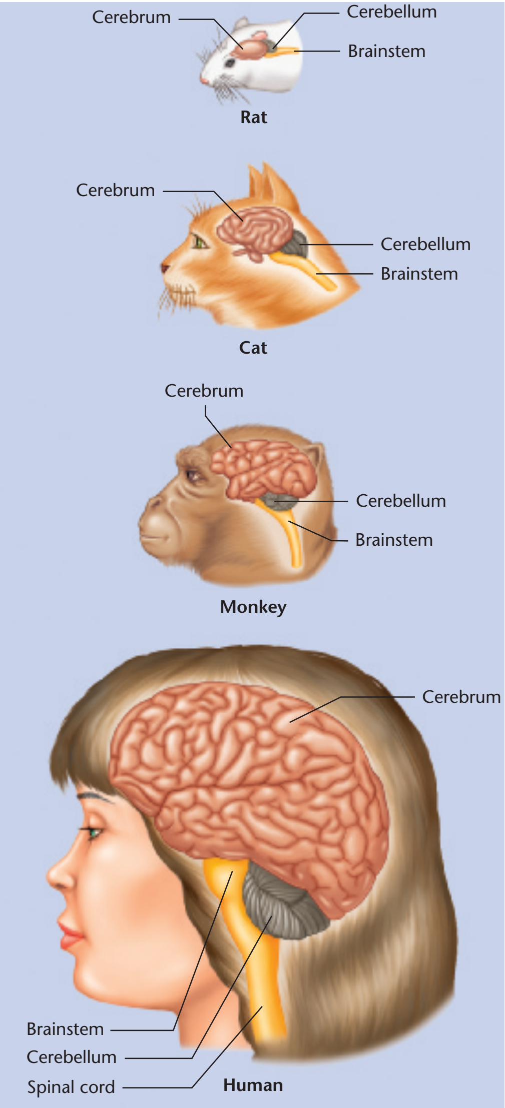
Louise Murray/Science Source

Animals are used in many kinds of research studies, some dealing with behavior and others with the functions of the nervous systems. Here, a hand-reared gray wolf uses a touchscreen computer at the Wolf Science Center, Austria. This wolf has been trained to observe a split screen and count the number of dots shown. It indicates which of the two screens shows the most number of dots by touching it with its nose. The wolf is able to complete the task at rapid speed and receives a food reward for each correct answer.

1. *Many of the mechanisms of behavior are similar across species, and sometimes they are easier to study in a nonhuman species.* If you want to understand a complex machine, you might begin by examining a simpler machine. We also learn about brain–behavior relationships by starting with simpler cases. Much research has been conducted on squid nerves, which are thicker than human nerves and therefore easier to study. The roundworm *Caenorhabditis elegans* has only 302 neurons, the same for all individuals, enabling researchers to map all the cells and all their interconnections. The sea slug *Aplysia* also has neurons that are almost always the same, including many large ones that are easy to study. Many vertebrates also have brains that are easy to study, and their brains resemble human brains in many regards (Figure 1.5).

Figure 1.5 Brains of several species

The general plan and organization of the brain are similar for all mammals, even though the size varies from species to species.



2. *We are interested in animals for their own sake.* Humans are naturally curious. We would like to understand how bats chase insects in the dark, how migratory birds find their way over unfamiliar territory, how schools of fish manage to swim in unison, and much more.
3. *What we learn about animals sheds light on human evolution.* How do we resemble chimpanzees and other primates, and how do we differ from them? Why and how did primates evolve larger brains than other species?
4. *Legal or ethical restrictions prevent certain kinds of research on humans.* Investigators sometimes insert electrodes into the brains of rats and other animals to determine the relationship between brain activity and behavior. They also inject chemicals, extract brain chemicals, and study the effects of brain damage. Such experiments answer questions that investigators cannot address in any other way, including some questions that are critical for medical progress. However, they do raise an ethical issue: When a research study is unacceptable with humans, is it acceptable with other species? If so, under what circumstances?

Stop & Check

2. Describe reasons biological psychologists conduct much of their research on nonhuman animals.

See page 13 for the answer.

Research raises no objections when investigators simply observe how animal behavior varies as a function of times of day, seasons of the year, changes in diet, and so forth. In other studies, however, including many discussed in this book, animals have been subjected to procedures that are clearly harmful to them. Anyone with a conscience, including scientists, is distressed by this fact. Nevertheless, experimentation with animals has been critical to the medical research that led to methods for the prevention or treatment of polio, diabetes, measles, smallpox, massive burns, heart disease, and other serious conditions. Retinal implants to alleviate blindness and cochlear implants for hearing loss began with animal research. Progress toward treating or preventing AIDS, Alzheimer's disease, Parkinson's disease, stroke, and other disorders depends largely on animal research. In much of medicine and biological psychology, research would progress slowly or not at all without animals.

Degrees of Opposition

Opposition to animal research ranges in degree. "Minimalists" accept certain types of animal research but not others depending on the probable value of the research, the amount of distress to the animal, and the type of animal. Few people have serious qualms about hurting an insect, for example. They favor firm regulations on research. Researchers agree in principle, although they often differ in where they draw the line between acceptable and unacceptable research. Comparing probable harm to benefits is difficult, and research often fails to live up to the optimistic expectations (Shriver and John, 2019).

The legal standard emphasizes "the three Rs": *reduction* of animal numbers (using fewer animals), *replacement* (using computer models or other substitutes for animals, when possible), and *refinement* (modifying the procedures to reduce pain and discomfort). In the United States, every college or other institution that receives government research funds is required to have an Institutional Animal Care and Use Committee, composed of veterinarians, community representatives, and scientists that evaluate proposed experiments, decide whether they are acceptable, and specify procedures to minimize pain and discomfort. Similar regulations and committees govern research on human subjects. In addition, research laboratories must abide by national laws requiring standards of cleanliness and animal care. Scientific journals accept publications only after researchers state that they followed all the laws and regulations. Professional organizations such as the Society for Neuroscience publish guidelines for the use of animals in research (refer to Appendix B). Rules differ from one country to another. For example, research on treatments for Ebola, Zika, and other viruses requires studies on monkeys, but political pressures in the United States and Europe block nearly all such research, leaving the world to rely on researchers in China, where the government is more permissive ("Monkeying around," 2016).

In contrast to "minimalists," the "abolitionists" find no room for compromise. Abolitionists maintain that all animals have the same rights as humans. They regard killing an animal as murder, regardless of whether the intention is to eat it, use its fur, or gain scientific knowledge. Keeping an animal in a cage (presumably even a pet) is, in their view, slavery. Because animals cannot give informed consent to research, abolitionists insist it is wrong to use them in any way, regardless of the circumstances. According to one opponent of animal research, "We have no moral option but to bring this research to a halt. Completely. . . . We will not be satisfied until every cage is empty" (Regan, 1986, pp. 39–40). Advocates of this position sometimes claim that most animal research is painful and that it never leads to important results. However, for a true abolitionist, neither of those points matters. Their moral imperative is that people have no right to use animals at all, even if the research is highly useful and totally painless.

The disagreement between abolitionists and animal researchers is a dispute between two ethical positions: "Never knowingly harm an innocent" and "Sometimes a little harm leads to a greater good." On the one hand, permitting research has the undeniable consequence of inflicting pain or distress. On the other hand, banning all use of animals would mean a great setback in medical research as well as the end of animal-to-human transplants (e.g., transplanting pig heart valves to prolong lives of people with heart diseases). Medical researchers and brain researchers would welcome the day when they can do without animal research, but that day is not at hand (Homberg et al., 2021).

It would be nice to say that this ethical debate has always proceeded in an intelligent and mutually respectful way. Unfortunately, it has not. Over the years, abolitionists have sometimes advanced their cause through intimidation. Examples include vandalizing laboratories, placing a bomb under a professor's car, placing a bomb on a porch (intended for a researcher but accidentally placed on the neighbor's porch), banging on a researcher's children's windows at night, and inserting a garden hose through a researcher's window to flood the house (G. Miller, 2007a). Michael Conn and James Parker (2008, p. 186) quote a spokesperson for the Animal Defense League as follows: "I don't think you'd have to kill—assassinate—too many [doctors involved with animal testing]. . . . I think for 5 lives, 10 lives, 15 human lives, we could save a million, 2 million, 10 million nonhuman lives." One researcher, Dario Ringach, finally agreed to stop his research on monkeys, if animal-rights extremists would stop harassing and threatening his children. He emailed them, "You win." In addition to researchers who quit in the face of attacks, many colleges and other institutions have declined to open animal research laboratories because of their fear of violence. Researchers have replied to attacks with campaigns such as the one illustrated in Figure 1.6.

The often fervent and extreme nature of the opposition makes it difficult for researchers to express intermediate or nuanced views. Many of them remark that they really do care about animals, despite using them for research. Some neuroscientists are vegetarians (Marris, 2006). But admitting to doubts seems almost like giving in to intimidation. The result is extreme polarization that interferes with open-minded contemplation of the difficult issues.

We began this chapter with a quote from the Nobel Prize-winning biologist Niko Tinbergen, who argued that no fundamental gulf separates humans from other animal species. Because we are similar in many ways to other species, we learn much about ourselves from animal studies. Also because of that similarity, we wish not to hurt them. Neuroscience researchers who decide to conduct animal research do not, as a rule, take the decision lightly. They believe it is better to inflict distress under controlled conditions than to permit ignorance and disease to inflict greater distress. In some cases, however, it is a difficult decision.

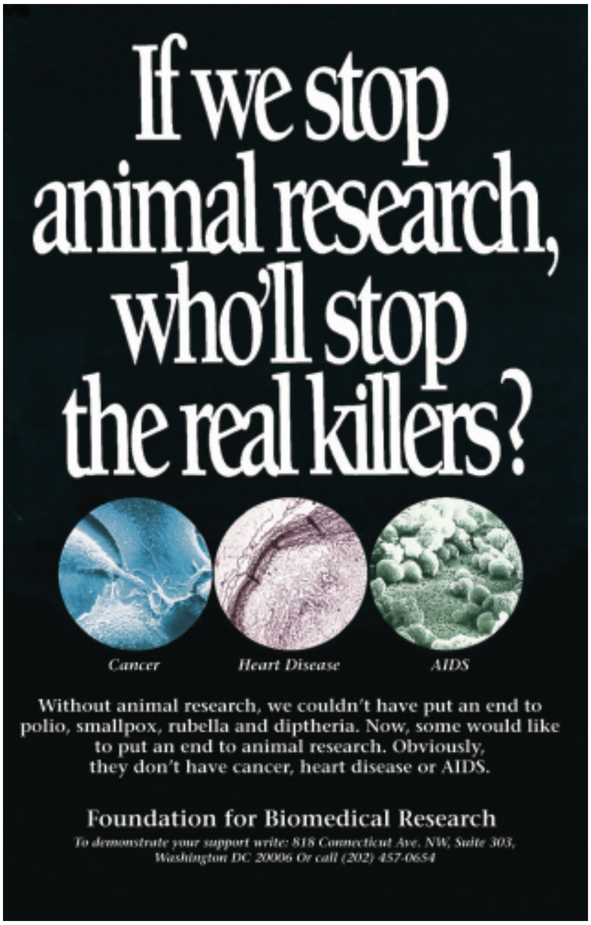
Stop & Check

3. What are the "three Rs" in the legal standards for animal research?
4. How does the "minimalist" position differ from the "abolitionist" position?

See page 13 for the answer.

Figure 1.6 In defense of animal research

For many years, opponents of animal research have been protesting against experimentation with animals. This ad defends such research.


If we stop animal research, who'll stop the real killers?
Cancer
Heart Disease
AIDS

Without animal research, we couldn't have put an end to polio, smallpox, rubella and diptheria. Now, some would like to put an end to animal research. Obviously, they don't have cancer, heart disease or AIDS.

Foundation for Biomedical Research

To demonstrate your support write: 818 Connecticut Ave. NW, Suite 303, Washington DC 20006 Or call (202) 457-0654

Courtesy of the Foundation for Biomedical Research

(**Source:** Courtesy of the Foundation for Biomedical Research)

Issues in Human Research

Research with humans raises different types of ethical concerns. Brain surgery is sometimes conducted while a person is under only local anesthesia, and therefore awake. (The skin of the scalp has pain receptors, but the brain itself does not.) Sometimes a patient undergoing such surgery is invited to participate in a study where researchers will record from brain cells while presenting sensory stimuli. So far as we know, the procedure causes the patient no harm, but it also provides no benefit. The shaky part of the ethics is getting informed consent. If your surgeon asked you to participate, would you say yes, just to please your surgeon?

Another issue: Sometimes a patient with Parkinson's disease has electrodes implanted to stimulate areas deep in the brain, after other types of treatment have failed. The procedure is usually successful, and usually without any serious negative effects, but occasionally the person shows troublesome behavioral changes. When that happens, is

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the individual personally responsible for the misbehavior? Or is it the fault of the electrodes (Mosley et al., 2021)?

Yet another concern: Because most research has been done in North America or Europe, most studies of humans have used relatively prosperous people, mostly people of European ancestry, not a representative sample of all humanity. For some purposes, that is not a problem. Brain anatomy is the same for people throughout the world. The basic principles of neurons, synapses, and sensory organs are the same for all people, and in some respects almost the same for all mammals. Where diversity, or the lack of it, becomes a big issue is the effects of medications. Some medications affect people differently because of small changes in their genetics. Some medications affect females differently from males. Several pharmaceutical companies have faced complaints, even lawsuits, because they marketed a drug after testing it on only one type of person (Boden-Albala, 2022). One excuse for not using a broader sample has been researchers' assumption that minority group members would refuse, because they knew about past cases of abuse. An especially shameful example was the Tuskegee study from 1932 to 1972, in which investigators knowingly failed to treat syphilis in Black men, just to observe how the disease progressed. However, researchers have found that minority group members are mostly willing to participate, if they are given proper explanations about the proposed research (Boden-Albala, 2022).

Stop & Check

5. Why is diversity an important issue for some types of research on humans, and less for others?

See page 13 for the answer.

Module 1.1 | In Closing

Your Brain and Your Experience

Biological psychologists are ambitious, hoping to explain as much as possible of psychology in terms of brain processes, genes, and evolutionary history. The guiding assumption is that the pattern of activity that occurs in your brain when you see or hear something *is* your perception. The pattern that occurs when you feel fear or anger *is* your emotion. The rest of this book explores how far we can go with this guiding assumption.

Summary

1. Two profound, difficult questions are why the universe exists and why consciousness exists. Regardless of whether these questions are answerable, they motivate research on related topics. **4**
2. Three key points are important to remember: First, perception occurs in your brain, not in your skin or in the object you see. Second, as far as we can tell, brain activity is inseparable from mental activity. Third, brain differences explain many ways in which people differ from one another. **5**
3. Biological psychologists address four types of questions about any behavior. Physiological: How does the behavior relate to the physiology of the brain and other organs? Ontogenetic: How does it develop within the individual? Evolutionary: How did the capacity for the behavior evolve? Functional: Why did the capacity for this behavior evolve? That is, what function does it serve or did it serve? **6**
4. Many careers relate to biological psychology, including various research fields, certain medical specialties, and counseling and psychotherapy. **8**
5. Researchers study animals because the mechanisms are sometimes easier to study in nonhumans, because they are interested in animal behavior for its own sake, because they want to understand the evolution of behavior, and because certain kinds of experiments are difficult or impossible with humans. **9**
6. Using animals in research is ethically controversial. Some research does inflict stress or pain on animals; however, many research questions can be investigated only through animal research. **10**
7. Animal research today is conducted under legal and ethical controls that attempt to minimize animal distress. **10**
8. Ethical issues in human research include being sure that informed consent is truly voluntary, and getting a diverse sample of people for research trials on medications. **11**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

biological psychology	**5**
dualism	**5**
evolutionary explanation	**6**
functional explanation	**6**
mind–body or mind–brain problem	**4**
monism	**5**
ontogenetic explanation	**6**
physiological explanation	**6**

Thought Questions

Thought questions are intended to spark thought and discussion. In most cases, there is no clearly right answer.

1. Is consciousness useful? What, if anything, can we do because of consciousness that we couldn't do otherwise?
2. What are the special difficulties of studying the evolution of behavior, given that behavior doesn't leave fossils (with a few exceptions such as footprints showing an animal's gait)?

Stop & Check Answers

1. An evolutionary explanation states what evolved from what. For example, humans evolved from earlier primates and therefore have certain features that we inherited from those ancestors, even if the features are not useful to us today. A functional explanation states why something was advantageous and therefore favored by natural selection.
2. Sometimes the mechanisms of behavior are easier to study in a nonhuman species. We are curious about animals for their own sake. We study animals to understand human evolution. Certain procedures that might lead to important knowledge are illegal or unethical with humans.
3. Reduction, replacement, and refinement.
4. A "minimalist" wishes to limit animal research to studies with little discomfort and much potential value. An "abolitionist" wishes to eliminate all animal research regardless of how the animals are treated or how much value the research might produce.
5. The basic aspects of brain anatomy, nerve cells, synapses, and sensory function are the same for people throughout the world, and even for most other mammalian species. However, the effects of medications often differ based on people's genes, and sometimes differ between males and females.

Module 1.1 | End-of-Module Quiz

1. What is meant by "monism"?
   - **a.** The idea that all forms of life evolved from a single ancestor
   - **b.** The idea that conscious and unconscious motivations combine to produce behavior
   - **c.** The idea that the mind is made of the same substance as the rest of the universe
   - **d.** The idea that the mind is one type of substance as matter is another

2. An ontogenetic explanation focuses on which of the following?
   - **a.** How a behavior develops
   - **b.** The brain mechanisms that produce a behavior
   - **c.** The conscious experience that accompanies a behavior
   - **d.** The procedures that measure a behavior

3. Of the following, which one is an example of an evolutionary explanation (as opposed to a functional explanation)?
   - **a.** People evolved a fear of snakes because many snakes are dangerous.
   - **b.** Humans have a (tiny) tailbone because our ancient monkey-like ancestors had a tail.
   - **c.** People evolved an ability to recognize faces because that ability is essential for cooperative social behaviors.
   - **d.** People evolved a tendency to form long-term male–female bonds because human infants benefit from the help of two parents during their long period of dependence.

4. Which of the following would be most likely to work in a hospital or clinic?
   - **a.** Behavioral neuroscientist
   - **b.** Comparative psychologist
   - **c.** Evolutionary psychologist
   - **d.** Neuropsychologist

5. What does a "minimalist" favor with regard to animal research?
   - **a.** All research should have a minimum of at least 10 animals per group.
   - **b.** A minimum of three people should review each research proposal.
   - **c.** Interference with animal research should be held to a minimum.
   - **d.** Animal research is permissible but should be held to a minimum.

Answers: 1c, 2a, 3b, 4d, 5d.

Module 1.2

Neurons and Other Cells

Learning Objectives

After studying this chapter, you should be able to:

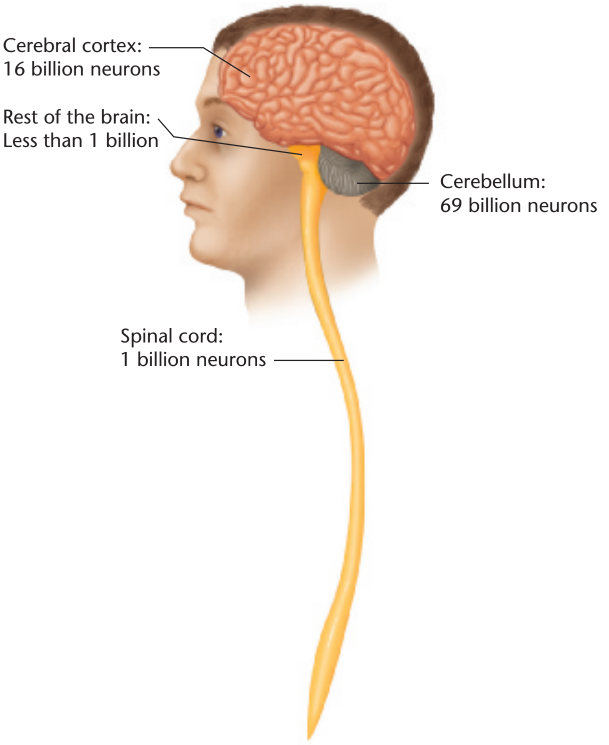
5. Describe neurons and glia, the cells that constitute the nervous system.
6. Contrast axons with dendrites.
7. Summarize how the blood–brain barrier relates to protection and nutrition of neurons.
8. State the chemicals necessary for the brain's nutrition.
9. Describe the importance of the bacteria in the intestines.

You think of yourself as an individual. You don't think of your mental experience as being composed of pieces, but it depends on the activity of a huge number of separate but interconnected cells. One cell by itself is helpless, but combined with the others, it becomes part of a process that accomplishes great things.

We begin our study of the nervous system by examining single cells. In these first chapters, you may wonder what all this biology has to do with psychology. Just as you had to learn the alphabet before you could learn to read, you need to understand neurons and their connections before you can understand how they produce behaviors and experiences. *Advice:* Parts of this chapter and the next assume that you understand some basic chemistry. If have never studied chemistry or if you need a refresher, review Appendix A.

Figure 1.7 Estimated numbers of neurons in humans

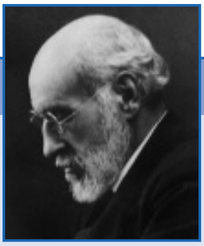
The numbers differ from one person to another.



(**Source:** Based on data from Herculano-Houzel et al., 2015)

Neurons

The nervous system consists of two kinds of cells, neurons and glia. **Neurons** receive information and transmit it to other cells. We consider glia later in this module. According to the best estimate, the adult human brain contains approximately 86 billion neurons, on average (Herculano-Houzel et al., 2015; Figure 1.7). However, that number is



Bettmann/Getty Images

Santiago Ramón y Cajal (1852–1934)

How many interesting facts fail to be converted into fertile discoveries because their first observers regard them as natural and ordinary things! . . . It is strange to see how the populace, which nourishes its imagination with tales of witches or saints, mysterious events and extraordinary occurrences, disdains the world around it as commonplace, monotonous and prosaic, without suspecting that at bottom it is all secret, mystery, and marvel. (Cajal, 1937, pp. 46–47)

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just an average. People vary in their neuron numbers more than they vary in their height (von Bartheld et al., 2016).

Santiago Ramón y Cajal, a Pioneer of Neuroscience

Two scientists of the late 1800s and early 1900s, who knew each other well, pioneered the field of neuroscience: Charles Sherrington, whom we shall discuss in the chapter on synapses, and Santiago Ramón y Cajal (1852–1934). Cajal's early education did not progress smoothly. At one point, he was imprisoned in a solitary cell, limited to one meal a day, and taken out daily for public floggings—at the age of 10—for the crime of not paying attention during his Latin class (Cajal, 1901–1917/1937). (And *you* complained about *your* teachers!)

Cajal wanted to become an artist, but his father insisted that he study medicine as a safer way to make a living. He managed to combine the two fields, using his drawing skills to illustrate his medical research. His detailed drawings of the nervous system are still considered definitive today. One of his major contributions was an idea that we now take for granted—the idea that the brain consists of individual cells.

During the 1800s biologists discovered that the body consists of cells, but at first, they were not sure that the same was true of the brain. In the rest of the body, microscopes revealed cells that were either roundish or elongated. When biologists examined at the brain, they found peculiar shapes that looked nothing like the other cells, with long fibers stretching from one place to another. Were those weird-looking things really cells? Or was the brain different from the rest of the body? Maybe everything in the brain joined together in a single mesh.

At first, microscopes did not provide enough detail to answer the question. Then, in the late 1800s, the Italian investigator Camillo Golgi found a way to stain nerve cells with silver salts. This method, which completely stains some cells without affecting others at all, enabled researchers to examine the structure of a single cell. Using this method to examine the brain, Golgi concluded that the fibers of the brain all link together. That is, he concluded that the brain is like a mesh, without separate cells.

Spanish investigator Cajal used Golgi's staining method, but he applied it to infant brains, in which the cells are smaller and easier to examine on a single slide. He came to the opposite conclusion: Nerve cells remain separate instead of merging into one another. A small gap separates the tip of a neuron's fiber from the surface of the next neuron. The brain, like the rest of the body, does indeed consist of individual cells.

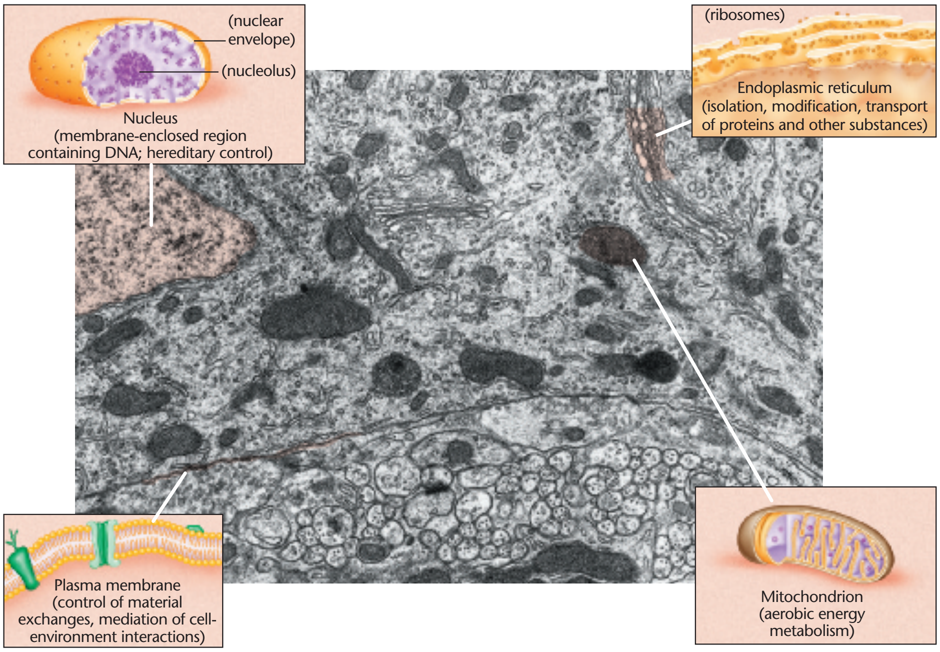
In 1906, Cajal and Golgi shared the 1906 Nobel Prize for Physiology or Medicine. Cajal used his acceptance speech to outline the cellular basis of the brain. In spite of Cajal's evidence, which had persuaded almost everyone else, Golgi continued to defend the theory that all nerve cells merge directly into one another. It was the only time in history when those who shared a Nobel prize used the occasion to give acceptance speeches that contradicted each other.

The Structures of an Animal Cell

Figure 1.8 illustrates a neuron from the cerebellum of a mouse (magnified enormously). Neurons have much in common with the rest of the body's cells. The surface of a cell is its **membrane** (or *plasma membrane*), a structure that separates the inside of the cell from the outside environment. Most chemicals cannot cross the membrane, but

Figure 1.8 An electron micrograph of parts of a neuron from the cerebellum of a mouse

The nucleus, membrane, and other structures are characteristic of most animal cells. The plasma membrane is the border of the neuron. Magnification approximately x 20,000.


(nuclear envelope)
(nucleolus)
Nucleus
(membrane-enclosed region containing DNA; hereditary control)
(ribosomes)
Endoplasmic reticulum
(isolation, modification, transport of proteins and other substances)
Plasma membrane
(control of material exchanges, mediation of cell-environment interactions)
Mitochondrion
(aerobic energy metabolism)

Courtesy of Dr. Dennis M.D. Landis

(**Source:** Micrograph courtesy of Dennis M. D. Landis) protein channels in the membrane permit a controlled flow of water, oxygen, sodium, potassium, calcium, chloride, and other important chemicals.

Except for mammalian red blood cells, all animal cells have a **nucleus**, the structure that contains the chromosomes. The chromosomes do not just float around loosely. DNA, the chemical that forms the chromosomes, is not stable for long in water solution. The DNA and other key chemicals are carefully scaffolded by other molecules.

Cells also contain **ribosomes**, structures that synthesize new protein molecules. Some ribosomes float freely within the cell, but others attach to the **endoplasmic reticulum**, a network of thin tubes that transport newly synthesized proteins to other locations.

A **mitochondrion** (plural: mitochondria) performs metabolic activities, providing the energy that the cell uses for all activities. For many years, neuroscientists and psychologists paid little attention to mitochondria, but later research has increased their interest. Mitochondria are not all the same. Mitochondria have their own genes, separate from those in the nucleus of a cell. Mitochondria are inherited in the cytoplasm of the egg cell. Therefore, you inherited your mitochondria from your biological mother, who got them from her mother, and so on.

Because brain activity requires more energy than the activity of any other organ, the brain is especially dependent on good mitochondrial functioning. Healthy mitochondria promote health, brain activity, and cognition (Geary, 2019). Mitochondria can be less active than average either because of genes within the mitochondria themselves or because of toxic chemicals, stress, or illnesses that produce inflammation. Decreased mitochondrial function means decreased mental energy and a high probability of depression (Chen et al., 2017; Fernandez et al., 2019). Impairments of mitochondria have also been linked to increased severity of epilepsy, Alzheimer's disease, Parkinson's disease, and Huntington's disease (Andreasen and Nedergaard, 2021; Devine and Kittler, 2018; Muddapu et al., 2020).

Stop & Check

6. Why would weakened mitochondria affect the brain more than other organs?

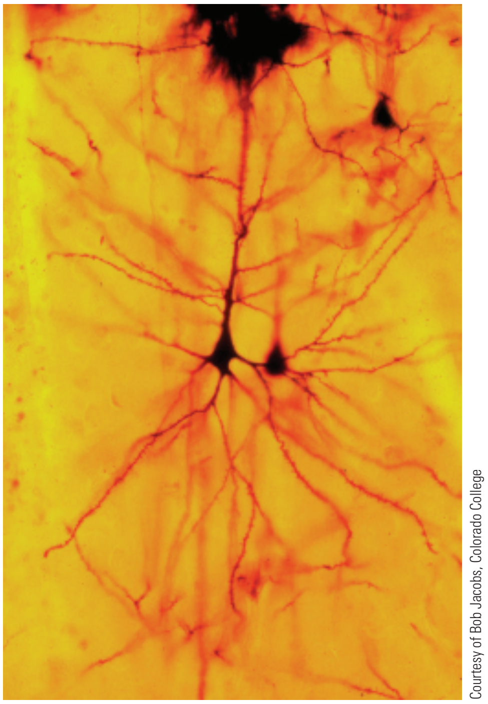
See page 23 for the answer.

The Structure of Neurons

Compared to other cells, the most distinctive feature of neurons is their highly variable shape (Figure 1.9). All neurons include a soma (cell body), and most also have dendrites, an axon, and presynaptic terminals. The tiniest neurons lack axons, and some neurons lack well-defined dendrites. Contrast the motor neuron in Figure 1.10 and the sensory neuron in Figure 1.11. A **motor neuron**, with its soma in the spinal cord, receives excitation through its dendrites and conducts impulses along its axon to a muscle. A **sensory neuron** is specialized at one end to be highly sensitive to a particular type of stimulation, such as touch. The sensory neuron depicted in Figure 1.11 conducts touch information from the skin to the spinal cord. Tiny branches lead directly from the receptors into the axon, and the cell's soma is located on a little stalk off the main trunk.

Figure 1.9 Neurons, stained to appear dark

Note the small fuzzy-looking spines on the dendrites.



Courtesy of Bob Jacobs, Colorado College

(**Source:** Photo courtesy of Bob Jacobs, Colorado College)

Dendrites are branching fibers that get narrower near their ends. The term *dendrite* comes from a Greek root word meaning "tree." Giorgio Ascoli (2015) offers this analogy: If you expanded a dendrite to the height of a tree, the dendrite would be as thick as your little finger, its branches would be as thin as spaghetti, and the cell's axon would extend for more than 25 city blocks.

The dendrite's surface is lined with specialized *synaptic receptors*, at which the dendrite receives information from other neurons. Many dendrites contain **dendritic spines**, short outgrowths that increase the surface area available for synapses (Figure 1.12).

The **cell body**, or **soma** (Greek for "body"; plural: somata), contains the nucleus, ribosomes, and mitochondria. Cell bodies of neurons range in diameter from 0.005 millimeter (mm) to 0.1 mm in mammals, and up to a millimeter in certain invertebrates. In many neurons, the cell body, like the dendrites, is covered with synapses.

Figure 1.10 The components of a vertebrate motor neuron

The cell body of a motor neuron is in the spinal cord. The parts are not drawn to scale. In reality, an axon is much longer in proportion to the soma.

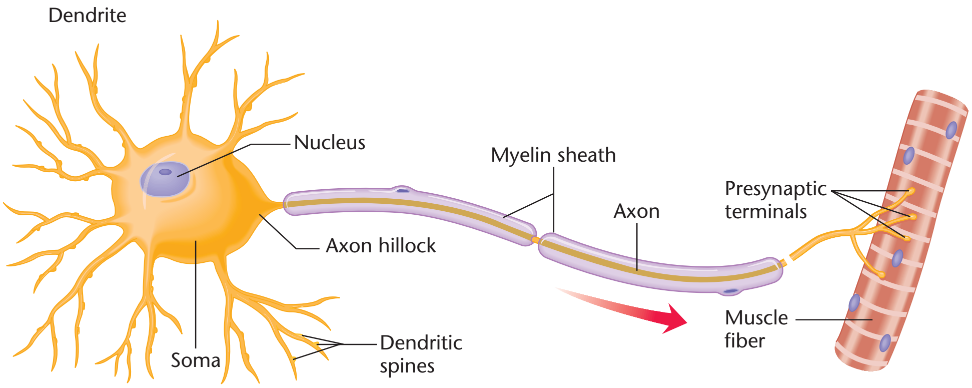
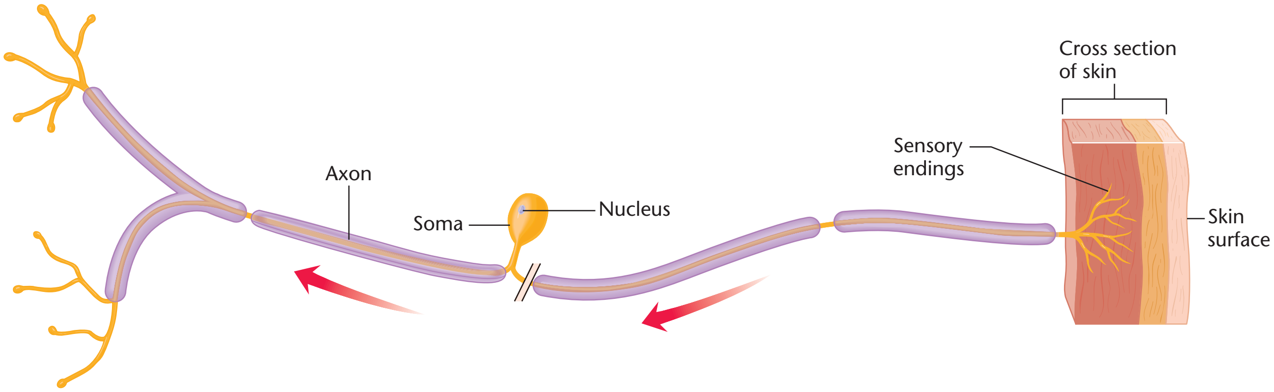


Figure 1.11 A vertebrate sensory neuron

Note that the soma is located on a stalk off the main trunk of the axon. (As in Figure 1.10, the structures are not drawn to scale.)



The **axon** is a thin fiber of constant diameter. The axon conveys an impulse to other neurons, an organ, or a muscle. Whereas dendrites are never more than a few millimeters long, some axons extend more than a meter, such as the axons from your spinal cord to your feet. An axon has branches near its end.

Many vertebrate axons are covered with an insulating material called a **myelin sheath** with interruptions known as **nodes of Ranvier** (RAHN-vee-ay). Invertebrate axons do not have myelin sheaths. Although a neuron can have many dendrites, it has only one axon, which may have branches. The end of each branch has a swelling, called a **presynaptic terminal**, also known as an *end bulb* or *bouton* (French for "button"). At that point the axon releases chemicals that cross to another cell.

Other terms associated with neurons are *afferent*, *efferent*, and *intrinsic.* An **afferent axon** brings information into a structure; an **efferent axon** carries information away from a structure. Every sensory neuron is an afferent to the nervous system, and every motor neuron is an efferent from the nervous system. Within the nervous system, any neuron is an afferent from one structure and an efferent to another (Figure 1.13). You can remember that *afferent* starts with *a* as in *admit*, and *efferent* starts with *e* as in *exit.* If a cell's dendrites and axon are entirely contained within a single structure, the cell is an **interneuron** or **intrinsic neuron** of the structure.

Stop & Check

7. How does the structure of a dendrite differ from that of an axon?
8. Which animal species would have the longest axons?
9. Of the three types of neuron—sensory, motor, and intrinsic—which would have the shortest axons?

See page 23 for the answer.

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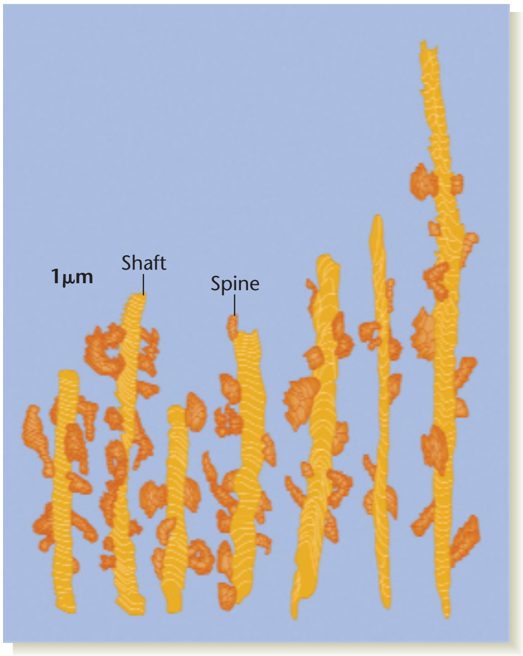
Figure 1.12 Dendritic spines

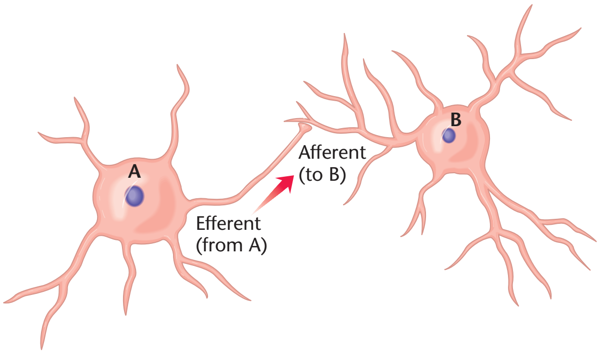
Many dendrites are lined with spines, short outgrowths that receive incoming information.



(**Source:** From K. M. Harris and J. K. Stevens, Society for Neuroscience, "Dendritic Spines of CA1 Pyramidal Cells in the Rat Hippocampus: Serial Electron Microscopy with Reference to Their Biophysical Characteristics." *Journal of Neuroscience, 9* (1989), 2982–2997. Copyright © 1989 Society for Neuroscience. Reprinted by permission.)

Figure 1.13 Cell structures and axons

It all depends on the point of view. An axon from A to B is an efferent axon from A and an afferent axon to B, just as a train from Washington to New York is exiting Washington and approaching New York.



Variations among Neurons

Neurons vary enormously in size, shape, and function. The shape of a neuron determines its connections with other cells and thereby determines its function (Figure 1.14). The widely branching dendrites of the Purkinje cell in the cerebellum (Figure 1.14a) enable it to receive input from up to 200,000 other neurons. By contrast, the tiny bipolar neurons in the retina (Figure 1.14d) might receive input from as few as two other cells.

Glia

Glia (or neuroglia), the other components of the nervous system, perform many functions (Figure 1.15). The term *glia*, derived from a Greek word meaning "glue," reflects early investigators' idea that glia served a function like glue, to hold the neurons together. Although that concept is obsolete, the term remains. At one time, neuroscientists believed that glia greatly outnumbered neurons. According to later, more accurate measurements, neurons slightly outnumber glia (von Bartheld, 2018). The ratio of neurons to glia varies from one brain area to another.

The brain has several types of glia. The star-shaped **astrocytes** wrap around the dendrites connecting to functionally related axons, as depicted in Figure 1.16. A single astrocyte might surround the tips of a few hundred dendrites. By surrounding a connection between neurons, an astrocyte shields it from chemicals circulating in the surround (Nedergaard and Verkhatsky, 2012). Also, by taking up the ions and transmitters released by axons and then releasing them back, an astrocyte helps synchronize closely related neurons, enabling their axons to send messages in waves (Martín et al., 2015). Astrocytes are therefore important for generating rhythms, such as your rhythm of breathing (Morquette et al., 2015). Astrocytes also dilate the blood vessels to bring more nutrients into the most active brain areas (Filosa et al., 2006; Takano et al., 2006).

According to a popular hypothesis known as the *tripartite synapse*, the tip of an axon releases chemicals that cause the neighboring astrocyte to release its own chemicals, thus modifying the message to the next neuron (Ben Achour and Pascual, 2012). In some brain areas, astrocytes respond to hormones and thereby influence neurons (Kim et al., 2014). They also control the critical period for modification of the visual cortex early in life (Ribot et al., 2021). In short, astrocytes are active partners of neurons.

Tiny cells called **microglia** act as part of the immune system, removing viruses and fungi from the brain. They proliferate after brain damage, removing dead or damaged neurons (Brown and Neher, 2014). Together with astrocytes, microglia prune ineffective synapses and adjust the effectiveness of others (Allen and Lyons, 2018). Pruning the inappropriate synapses is an important process. Either too much pruning or too little pruning during early development leads to developmental disorders (Neniskyte and Gross, 2017). Yet another function of microglia is to provide negative feedback to put the brakes on neuronal activity. A loss of microglia leads to seizures (Badimon et al., 2020).

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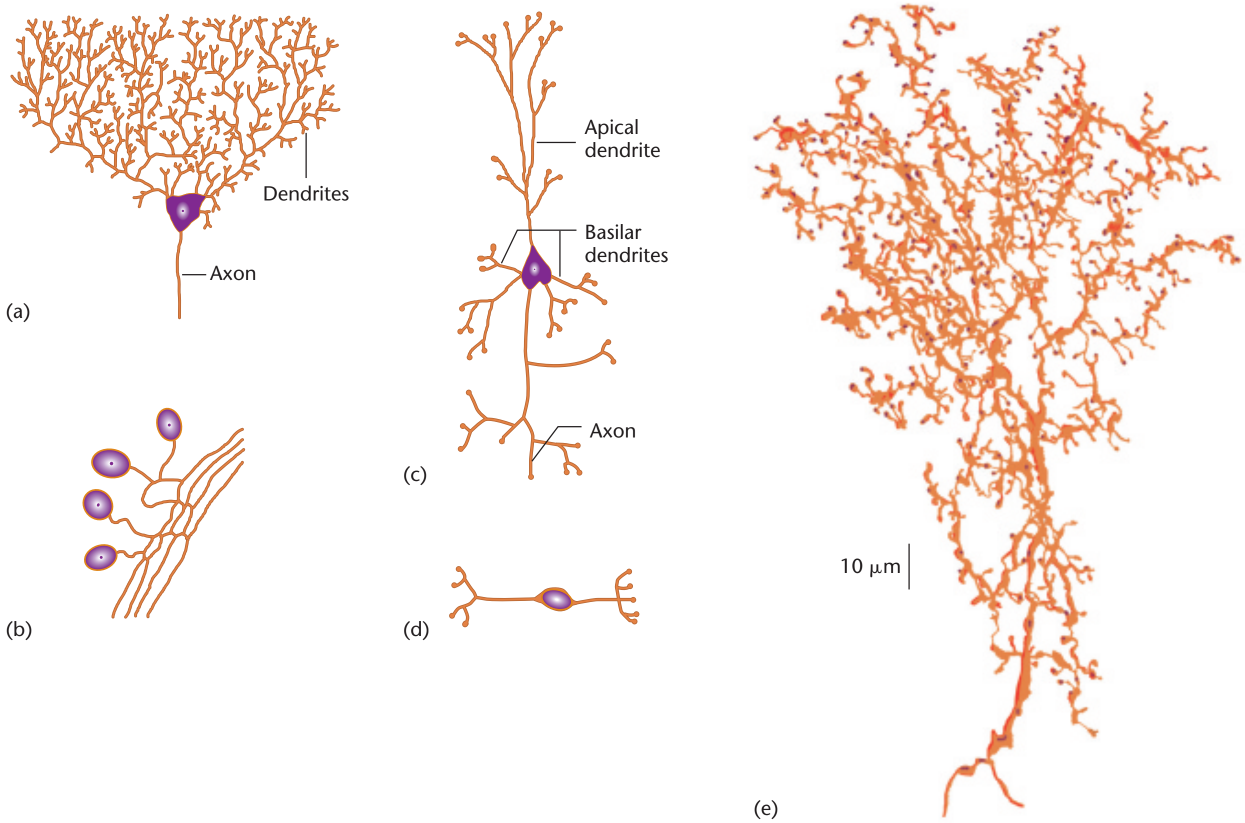

Figure 1.14 The diverse shapes of neurons

(a) Purkinje cell, a cell type found only in the cerebellum; (b) sensory neurons from skin to spinal cord; (c) pyramidal cell of the motor area of the cerebral cortex; (d) bipolar cell of retina of the eye; (e) Kenyon cell, from a honeybee.

(**Source:** Part e courtesy of R. G. Goss)

Oligodendrocytes (OL-i-go-DEN-druh-sites) in the brain and spinal cord and **Schwann cells** in the periphery of the body build the myelin sheaths that surround and insulate certain vertebrate axons. They also supply an axon with nutrients necessary for proper functioning (Y. Lee et al., 2012). Oligodendrocytes respond to neural activity by altering the myelin sheaths, thereby altering the timing of axons' responses. In that way they participate in certain types of learning and memory (Xin and Chan, 2020). **Radial glia** guide the migration of neurons and their axons and dendrites during embryonic development.

Stop & Check

10. Which type of glia synchronizes the activity of a related group of axons?
11. Which type of glia cell removes dead neurons and prunes ineffective synapses?

See page 23 for the answer.

The Blood–Brain Barrier

Although the brain, like any other organ, needs to receive nutrients from the blood, many chemicals cannot cross from the blood to the brain. The mechanism that excludes most chemicals from the vertebrate brain is known as the **blood–brain barrier**. First, let's consider why we need it.

Why We Need a Blood–Brain Barrier

When a virus invades a cell, mechanisms within the cell extrude virus particles through the membrane so that the immune system can find them. When the immune system cells find a virus, they kill it and the cell that contains it. In effect, a cell exposing a virus through its membrane says, "Look, immune system, I'm infected with this virus. Kill me and save the others."

This plan works well if the virus-infected cell is a skin cell or a blood cell, which the body replaces easily. However, with almost no exceptions, the vertebrate brain cannot replace damaged neurons. You can't afford to sacrifice brain

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Figure 1.15 Some glia cells

Oligodendrocytes produce myelin sheaths that insulate certain vertebrate axons in the central nervous system; Schwann cells have a similar function in the periphery. The oligodendrocyte is depicted here forming a segment of myelin sheath for two axons; in fact, each oligodendrocyte forms such segments for 30 to 50 axons. Astrocytes pass chemicals back and forth between neurons and blood and among neighboring neurons. Microglia proliferate in areas of brain damage and remove toxic materials. Radial glia (not depicted) guide the migration of neurons during embryological development. Glia have other functions as well.

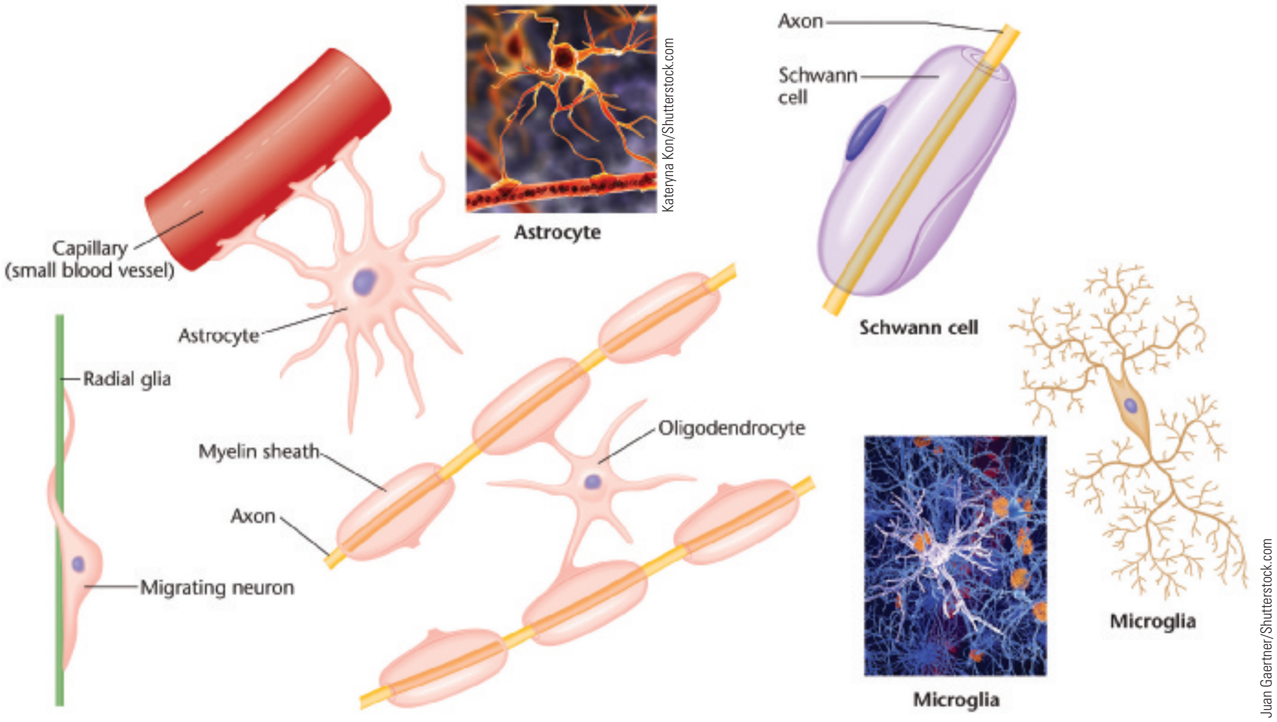
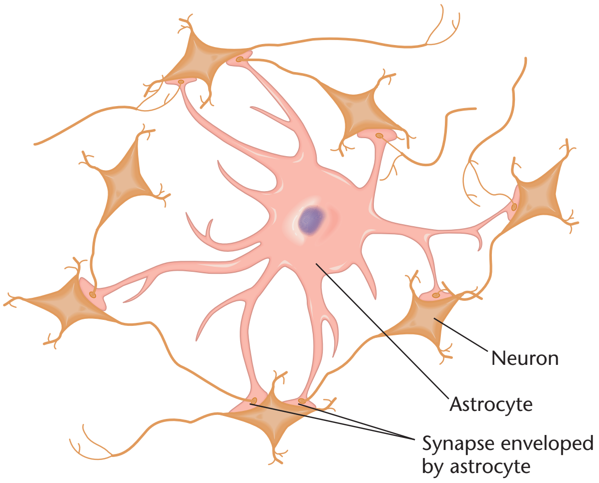


Figure 1.16 How an astrocyte synchronizes associated axons

Branches of the astrocyte (in the center) surround the presynaptic terminals of related axons. If a few of them are active at once, the astrocyte absorbs some of the chemicals they release. It then temporarily inhibits all the axons to which it is connected. When the inhibition ceases, all of the axons are primed to respond again in synchrony.



(**Source:** Based on Antanitus, 1998)

cells because of a viral infection. To minimize the risk, the body lines the brain's blood vessels with tightly packed cells that keep out most viruses and bacteria.

Unfortunately, a few viruses do cross the blood–brain barrier. What happens then? The brain's microglia attack most viruses that enter the nervous system, mounting an inflammatory response that fights the virus without killing the neuron (Ousman and Kubes, 2012). However, this response controls the virus without eliminating it. The spirochete responsible for syphilis can penetrate the blood–brain barrier, producing long-lasting and potentially fatal consequences if it is not properly treated. When the chicken pox virus enters spinal cord cells, virus particles remain there long after they have been exterminated from the rest of the body. The virus may emerge decades later, causing a painful condition called shingles. Similarly, the virus responsible for genital herpes hides in the nervous system, producing little harm there but periodically emerging to cause new genital infections.

The COVID-19 virus crosses the blood–brain barrier in mice, although we do not yet know about humans (Rhea et al., 2021). We do know that some people infected with that virus develop seizures, confusion ("brain fog"), or impairments of vision, taste, and smell.

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Even if the virus does not cross the blood–brain barrier, it could harm the brain by constricting capillaries, thus decreasing blood flow to the brain, and by triggering a great increase in the immune response. When immune cells become highly abundant, some of them attack the body's organs, including the brain, instead of the virus itself (Marshall, 2021).

How the Blood–Brain Barrier Works

The blood–brain barrier (Figure 1.17) depends on the endothelial cells that form the walls of the capillaries (Bundgaard, 1986; Rapoport and Robinson, 1986). Outside the brain, cells along the capillaries are separated by small gaps, but in the brain, they join so tightly that they block almost anything from passage.

"If the blood–brain barrier is such a good defense," you might ask, "why don't we have similar walls around all our organs?" The answer is that the barrier keeps out useful chemicals as well as harmful ones. For these chemicals to cross the blood–brain barrier, the brain needs special mechanisms (Kaplan et al., 2020). Because the membrane is made of fats, chemicals that dissolve in fats cross freely through the cell wall. Examples include oxygen, carbon dioxide, vitamins A and D, and all the drugs that affect the brain—from antidepressants and other psychiatric drugs to marijuana and heroin. How fast a drug crosses the blood–brain barrier determines how fast it affects behavior. Chemotherapy drugs do not cross the blood–brain barrier, and that is a major reason why brain cancers are so difficult to treat.

Water crosses through special protein channels in the wall of the endothelial cells. Sodium, potassium, and chloride ions also cross through specific channels. The brain uses **active transport**, a protein-mediated process that expends energy, to pump glucose (the brain's main fuel), amino acids (the building blocks of proteins), omega-3 fatty acids, and several vitamins from the blood into the brain. The membrane also has mechanisms to transport ketones and several hormones into the brain (Segarra et al., 2021).

The blood–brain barrier is essential to health. It tends to become less efficient in old age, especially in people with Alzheimer's disease. The result is that some needed chemicals enter the brain more slowly than before, and some harmful chemicals enter more extensively than before (Yang et al., 2020; Zipser et al., 2006).

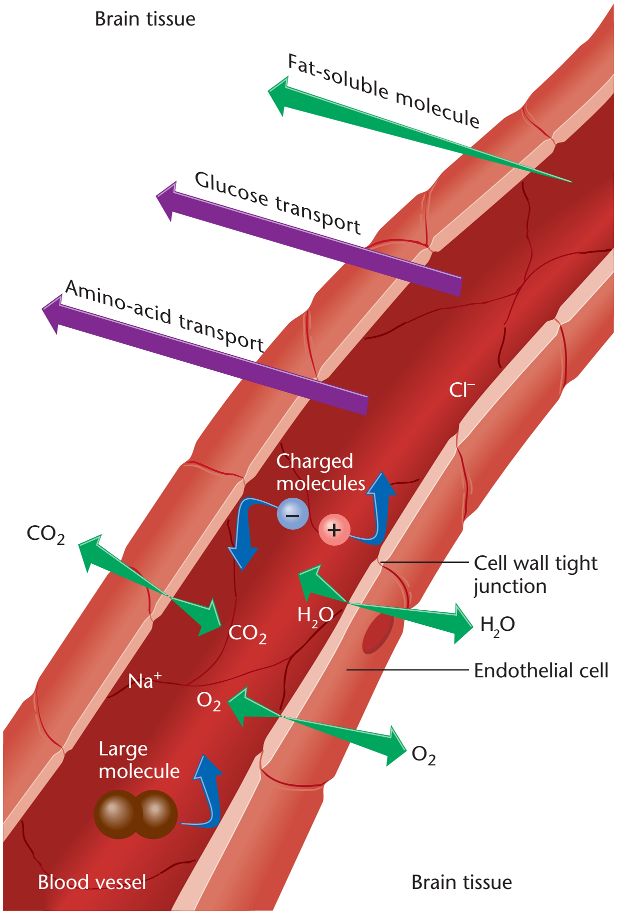
Stop & Check

12. Identify one major advantage and one disadvantage of having a blood–brain barrier.
13. Which chemicals cross the blood–brain barrier passively?
14. How do glucose and amino acids cross the blood–brain barrier?

See page 23 for the answer.

Figure 1.17 The blood–brain barrier

Most large molecules and electrically charged molecules cannot cross from the blood to the brain. Fat-soluble molecules, including oxygen and carbon dioxide, cross easily. Water, sodium, potassium, and chloride cross through narrow channels. Active transport systems pump glucose, amino acids, and several vitamins across the membrane.



Nourishment of Vertebrate Neurons

Most cells use a variety of carbohydrates and fats for nutrition, but vertebrate brain cells depend almost entirely on **glucose**. Cancer cells and the testis cells that make sperm also rely overwhelmingly on glucose. Brain cells also use ketones (a kind of fat) and lactate, but those fuels do not reach the brain in sufficient quantity to meet the needs. Because metabolizing glucose requires oxygen, neurons need a steady supply of oxygen. Although the human brain constitutes only about 2 percent of the body's weight, it uses about 20 percent of its oxygen and 25 percent of its glucose (Bélanger et al., 2011).

Glucose shortage is rarely a problem, except during starvation. The liver makes glucose from many kinds of carbohydrates and amino acids, as well as from glycerol,

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a breakdown product from fats. A more likely problem is an inability to *use* glucose. To use glucose, the body needs vitamin B_1, **thiamine**. Prolonged thiamine deficiency, common in chronic alcoholism, leads to death of neurons and a condition called *Korsakoff's syndrome,* marked by memory impairments.

Other Cells: The Gut Bacteria

Another influence on your behavior comes from cells that are not really you, genetically. They are "guests" in your body—the bacteria in your gut. It is difficult to get an accurate count of the number of cells in your body or the number of bacteria in your intestines—and, anyway, not worth the bother—but the best estimate is that the numbers are about equal, a one-to-one ratio, within the error of measurement (Sender et al., 2016).

Your gut bacteria include many species, which vary from person to person. Bacteria influence brain activity in several ways. One way is to stimulate the vagus nerve, which runs from the intestines to the brain. Another is to release chemicals that cross the lining of the intestines and enter the blood. Those chemicals include vitamins and amino acids, but they can also include chemicals that cause inflammation. The amount and type of chemicals that bacteria release affect your mood and motivations, including your motivations for food, sex, socialization, and abused drugs (Garcia-Caberizo et al., 2021).

Stress increases the type of bacteria that cause inflammation and mitochondrial damage. People with depression tend to have more of those bacteria, as well as less of the bacteria with anti-inflammatory effects (Chen and Vitetta, 2020; Jiang et al., 2015). Some antidepressant drugs attack bacteria. Given that people with depression have many inflammatory bacteria, attacking them can be beneficial. However, it is not a good idea to get rid of too many of your intestinal bacteria. Removing most or all bacteria causes an increase in anxiety and depression (Needham et al., 2020). When people take antibiotics to attack bacteria, the side effects often include depression and anxiety. "Probiotics" are diet supplements that contain "good" bacteria, and some authorities recommend them as part of a treatment program for depression (Evrensel and Tarhan, 2021).

Module 1.2 | In Closing

The Cells

Everything the brain does depends on the detailed anatomy of its neurons and glia. However, nothing in your experience or behavior follows from the properties of any one neuron. Our behavior emerges from the communication among neurons.

Another major point to remember from this module is that your behavior depends on influences that you might easily ignore. Vigorous cognitive activity and favorable mood depend on healthy mitochondria. They also depend on favorable influences from the bacteria in your intestines. Your psychology is fully integrated with the biology of the body.

Summary

1. Neurons receive information and convey it to other cells. The nervous system also contains *glia*, cells that enhance and modify the activity of neurons in many ways. **14**
2. In the late 1800s, Santiago Ramón y Cajal used newly discovered staining techniques to establish that the nervous system is composed of separate cells, now known as neurons. **14**
3. Neurons contain the same internal structures as other animal cells. Mitochondria, inherited from the mother, differ from one person to another, and vigorous mitochondria are necessary for cognitive activity and positive mood. **16**
4. Neurons have a cell body (or soma), dendrites, an axon with branches, and presynaptic terminals. Neurons' shapes vary greatly depending on their functions and their connections with other cells. **16**
5. The blood–brain barrier keeps many molecules out of the brain. It protects the nervous system from viruses and many dangerous chemicals. **19**
6. Small, uncharged molecules such as water, oxygen, and carbon dioxide cross the blood–brain barrier freely. So do molecules that dissolve in fats. Active transport proteins pump glucose, amino acids, and a few other chemicals into the brain and spinal cord. **21**
7. Neurons rely heavily on glucose, the only nutrient that crosses the blood–brain barrier in large quantities. They need thiamine (vitamin B_1) to use glucose. **21**
8. Bacteria in the intestines may produce either helpful or harmful chemicals. **22**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

active transport	**21**
afferent axon	**17**
astrocytes	**18**
axon	**17**
blood–brain barrier	**19**
cell body (soma)	**16**
dendrites	**16**
dendritic spines	**16**
efferent axon	**17**
endoplasmic reticulum	**16**
glia	**18**
glucose	**21**
interneuron	**17**
intrinsic neuron	**17**
membrane	**16**
microglia	**18**
mitochondrion	**16**
motor neuron	**16**
myelin sheath	**17**
neurons	**14**
nodes of Ranvier	**17**
nucleus	**16**
oligodendrocytes	**19**
presynaptic terminal	**17**
radial glia	**19**
ribosomes	**16**
Schwann cells	**19**
sensory neuron	**16**
soma	**16**
thiamine	**22**

Thought Question

Although heroin and morphine are similar in many ways, heroin exerts faster effects on the brain. What can we infer about those drugs with regard to the blood–brain barrier?

Stop & Check Answers

6. The brain uses more energy than any other organ.

7. An axon is longer, and its diameter is constant. A dendrite is no more than a few millimeters long, and it tapers toward its end.

8. The longest axons occur in the largest animals. For example, giraffes and elephants have axons that extend from the spinal cord to the feet, nearly 2 meters away.

9. Because an interneuron is contained entirely within one part of the brain, its axon is short.

10. Astrocytes.

11. Microglia.

12. The blood–brain barrier keeps out viruses and many harmful chemicals (an advantage) but it also keeps out most nutrients (a disadvantage).

13. Molecules that dissolve in fats enter passively. So do water and several ions for which the membrane has specific channels.

14. The membrane has proteins that actively transport glucose and amino acids into the brain.

Module 1.2 | End-of-Module Quiz

1. Santiago Ramón y Cajal clearly demonstrated which of the following?

- **a.** The nervous system is composed of separate cells.
- **b.** Neurons pass chemicals to communicate at junctions called synapses.
- **c.** Brain damage can produce highly specialized behavioral deficits.
- **d.** The organization of the brain is substantially the same in all mammalian species.

2. Which part of a neuron has the chromosomes?

- **a.** The axon
- **b.** The cell body
- **c.** The dendrites
- **d.** The synapse

3. What do the mitochondria do?

- **a.** They provide energy for the cell.
- **b.** They produce the myelin sheath that surrounds an axon.
- **c.** They surround and insulate the synapses.
- **d.** They create the blood–brain barrier.

4. How do dendrite differ from axons?

- **a.** Dendrites are covered with myelin.
- **b.** Dendrites are long and cylindrical.
- **c.** Dendrites have branches.
- **d.** Dendrites are short and tapered.

5. What do dendritic spines do?

- **a.** They synthesize proteins.
- **b.** They increase the surface area available for synapses.
- **c.** They hold the neuron in position.
- **d.** They metabolize fuels to provide energy for the rest of the neuron.

6. What does an afferent axon do?

- **a.** It controls involuntary behavior.
- **b.** It controls voluntary behavior.
- **c.** It carries output from a structure.
- **d.** It brings information into a structure.

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7. Which of the following is a function of astrocytes?
  - **a.** They conduct impulses over long distances.
  - **b.** They create new neurons to replace those lost in brain damage.
  - **c.** They synchronize the activity of a group of neurons.
  - **d.** They build myelin sheaths that surround and insulate axons.

8. Which of the following is a function of microglia?
  - **a.** They remove dead cells and weak synapses.
  - **b.** They build myelin sheaths that surround and insulate axons.
  - **c.** They conduct impulses over long distances.
  - **d.** They synchronize activity for a group of neurons.

9. Why are chemotherapy drugs ineffective against brain cancers?
  - **a.** Brain cancers spread more rapidly than other cancers.
  - **b.** Brain cancers produce chemicals that inactivate the chemotherapy drugs.
  - **c.** Chemotherapy drugs dissolve in the axon membranes.
  - **d.** Chemotherapy drugs do not cross the blood–brain barrier.

10. Which of these chemicals cross the blood–brain barrier by active transport?
  - **a.** Oxygen, water, and fat-soluble molecules
  - **b.** Glucose and amino acids
  - **c.** Proteins
  - **d.** Viruses

11. What is the brain’s main source of fuel?
  - **a.** Glucose
  - **b.** Glutamate
  - **c.** Proteins
  - **d.** DNA

12. Why does the brain need thiamine (vitamin B_1)?
  - **a.** To metabolize glucose
  - **b.** To build the blood–brain barrier
  - **c.** To build myelin sheaths
  - **d.** To use at the synapses

13. Under what condition do the intestinal bacteria produce more inflammatory chemicals?
  - **a.** During sleep
  - **b.** When the temperature of the environment has been increasing
  - **c.** After any larger than average meal
  - **d.** Under stressful conditions that might lead to depression

---

Answers: 1a, 2b, 3a, 4d, 5b, 6d, 7c, 8a, 9d, 10b, 11a, 12a, 13d.

Module 1.3

The Action Potential

Learning Objectives

After studying this chapter, you should be able to:

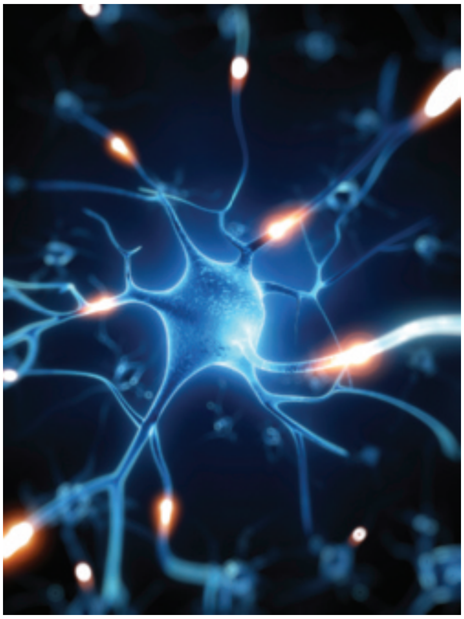
10. Contrast action potentials with electrical transmission.
11. Explain what causes the resting potential of a neuron.
12. Discuss how the movement of sodium and potassium ions produces the action potential and recovery after it.
13. State the all-or-none law of the action potential.
14. Explain how the action potential propagates along the axon.
15. Describe the importance of the refractory period, the myelin sheath, and local neurons.

Think about the axons that convey information from the touch receptors in your hands or feet toward your spinal cord and brain. If axons used electrical conduction, they could transfer information at a velocity approaching the speed of light. However, because your body is not made of copper wire, the strength of an impulse would decay rapidly as it traveled. A touch on your shoulder would feel stronger than a touch on your abdomen. Short people would feel their toes more strongly than tall people could—if either could feel their toes at all.

Axons function in a way that avoids that problem. Instead of conducting an electrical impulse, the axon periodically regenerates an impulse. Imagine a long line of people holding hands. The first person squeezes the second person's hand, who then squeezes the third person's hand, and so forth. The impulse travels along the line without weakening because each person generates it anew.

Figure 1.18 Structure of a neuron

A 3-d rendering of a magnified neuron or nerve cell



SciePro/Shutterstock.com

Although the axon's method of transmitting an impulse prevents a touch on your shoulder from feeling stronger than one on your toes, it introduces a different problem: Because axons transmit information at moderate speeds (varying from less than 1 meter/second to more than 100 m/s), a touch on your shoulder reaches your brain *sooner* than does a touch on your toes. The difference is small and generally unimportant.

In vision, however, your brain needs to know whether one stimulus began even slightly before or after another one. If light moves from point A on your retina to point B, then the input from A will reach your brain slightly before the input from B, and that difference tells you that something moved from A to B. But what if point A or B on the retina is slightly closer to the brain? If so, its input would reach the brain first, even if A and B were stimulated at the same time. To detect movement as accurately as possible, your visual system has the axons from more distant spots of the eye transmit slightly faster. If input from two parts of the eye start at the same time, they reach the brain at the same time, even if one part is slightly closer to the brain (Stanford, 1987)!

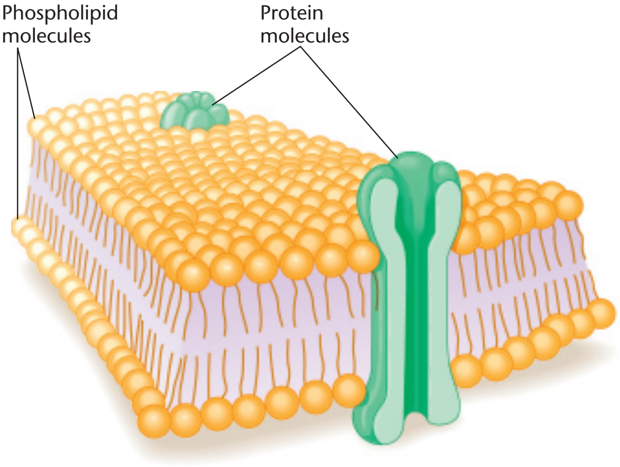
In short, the properties of impulse conduction in an axon are amazingly well adapted to your needs. Let's examine the mechanics of impulse transmission.

The Resting Potential of the Neuron

First, we need to consider the resting potential—the difference in electrical charge between the inside and the outside of a neuron. All parts of a neuron are covered by a membrane about 8 nanometers (nm) thick. That is about one ten-thousandth the width of a human hair. The membrane

Figure 1.19 The membrane of a neuron

Embedded in the membrane are protein channels that permit certain ions to cross through the membrane at a controlled rate.



is composed of two layers of phospholipid molecules (chains of fatty acids linked to a phosphate group). Embedded among the phospholipids are cylindrical proteins that let certain chemicals pass (Figure 1.19).

When at rest, the membrane maintains an **electrical gradient**, also known as **polarization**—a difference in electrical charge between the inside and outside of the cell. The inside of the membrane has a slight negative charge compared to the outside, mainly because of negatively charged proteins inside the cell. This difference in voltage is called the **resting potential**.

Researchers measure the resting potential by inserting a very thin *microelectrode* into the cell body, as in Figure 1.20. The most common electrode is a fine glass tube filled with a salt solution. A reference electrode outside the cell completes the circuit. Connecting the electrodes to a voltmeter, we find that the neuron's interior has a negative potential relative to its exterior. The magnitude varies, but a typical level is −70 millivolts (mV).

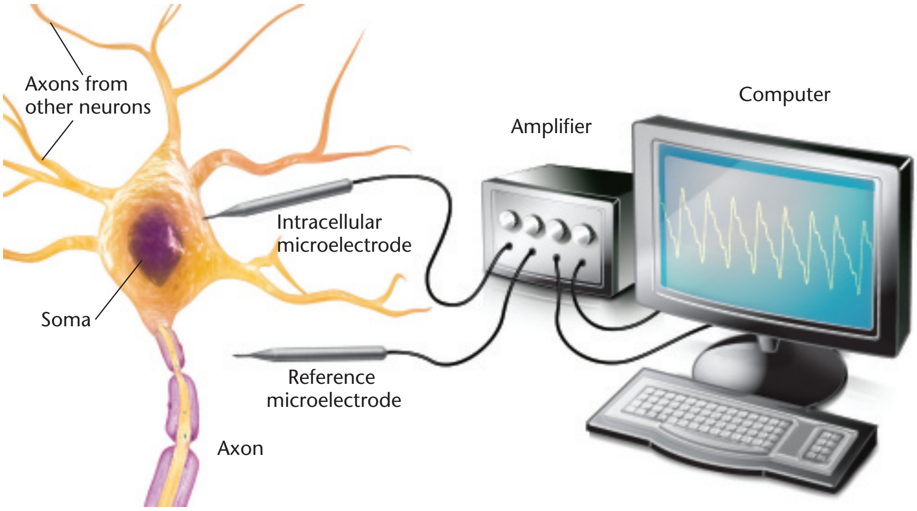
Forces Acting on Sodium and Potassium Ions

If charged ions could flow freely across the membrane, enough positive ions would enter to depolarize the membrane. However, the membrane is **selectively permeable**, letting some chemicals pass more freely than others. Oxygen, carbon dioxide, urea, and water are uncharged chemicals that cross freely through channels that are always open. Sodium, potassium, calcium, and chloride are charged ions that cross through channels (or gates) that are sometimes open and sometimes closed, as depicted in Figure 1.21. When the membrane is at rest, the sodium and potassium channels are closed, permitting almost no flow of sodium and only a small flow of potassium. Stimulation can open these channels, permitting freer flow.

The **sodium–potassium pump**, a protein complex, repeatedly transports three sodium ions out of the cell while drawing two potassium ions in. Because of this pump, sodium ions are more than 10 times more concentrated outside the membrane than inside, and potassium ions are more concentrated inside than outside.

Figure 1.20 Methods for recording activity of a neuron

Diagram of the apparatus and a sample recording.



(**Source:** Fritz Goro)

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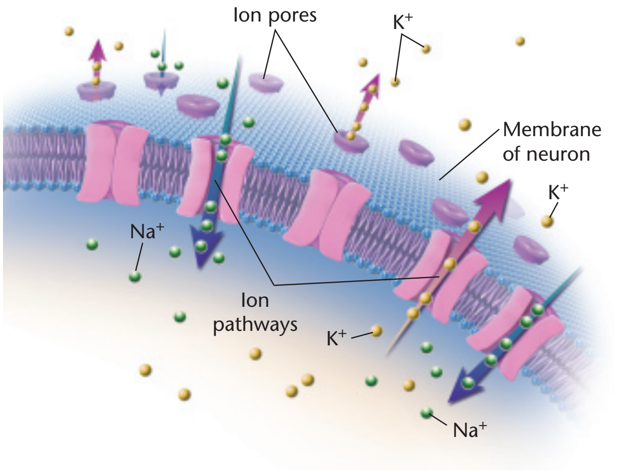
Figure 1.21 Ion channels in the membrane of a neuron

When a channel opens, it permits some type of ion to cross the membrane. When it closes, it blocks passage of that ion.

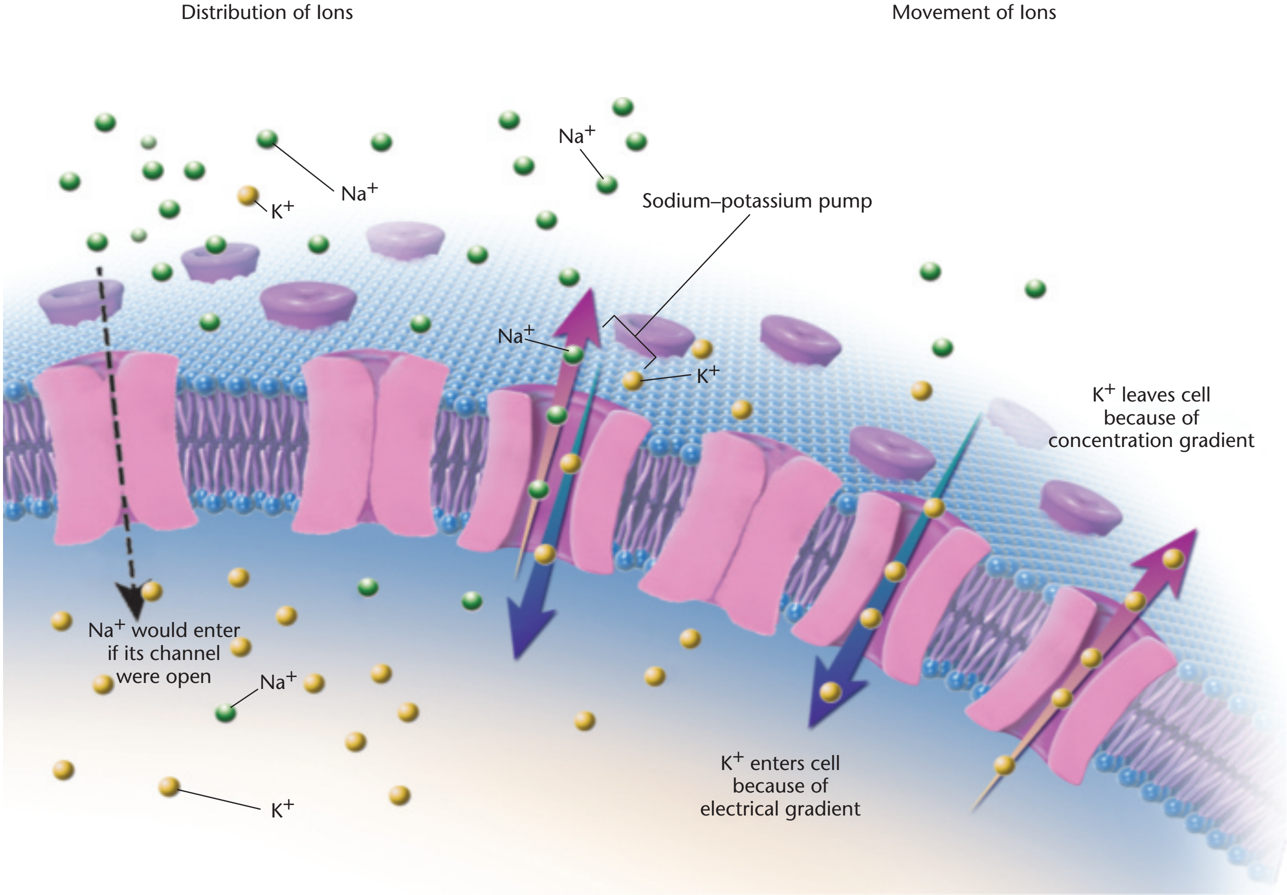

Ion pores
K+
Membrane of neuron
K+
Na+
Ion pathways
K+
Na+

The sodium–potassium pump is effective only because the selective permeability of the membrane prevents the sodium ions that were pumped out from leaking back in again. When sodium ions are pumped out, they stay out. However, some of the potassium in the neuron slowly leaks out, carrying a positive charge. That leakage increases the electrical gradient across the membrane, as depicted in Figure 1.22.

When the neuron is at rest, two forces tend to push sodium into the cell. One is the electrical gradient. Sodium is positively charged, and the inside of the cell is negatively charged, mainly because of negatively charged proteins. Opposite electrical charges attract, so the electrical gradient attracts sodium into the cell. The other force is the **concentration gradient**, the difference in distribution of ions across the membrane. Sodium is more concentrated outside than inside, so just by the laws of probability, it is more likely to enter the cell than to leave. Sodium would enter rapidly if it could, but the sodium channels are closed.

Figure 1.22 The sodium and potassium gradients for a resting membrane

The sodium–potassium pump keeps most sodium ions outside the neuron and most potassium ions inside. The sodium channels are closed. A small amount of potassium enters the cell because of the electrical gradient, and a small amount leaves because of the concentration gradient.


Distribution of Ions
Movement of Ions
Na+
K+
Na+
Sodium–potassium pump
Na+
K+
K+ leaves cell because of concentration gradient
Na+ would enter if its channel were open
Na+
K+
K+ enters cell because of electrical gradient

Potassium is subject to competing forces. Potassium is positively charged, and the inside of the cell is negatively charged, so the electrical gradient tends to attract potassium into the cell. However, potassium is more concentrated inside the cell than outside, so the concentration gradient tends to drive it out. (For an analogy, imagine many cats inside a room with food. The cats are attracted to the food, but when they get too crowded, some of them leave.) The potassium channels, almost completely closed, permit a small amount of potassium flow, more outward than inward, but the sodium–potassium pump continues pulling potassium back into the cell.

Stop & Check

15. When the membrane is at rest, are the sodium ions more concentrated inside the cell or outside? Where are the potassium ions more concentrated?
16. When the membrane is at rest, what tends to drive the potassium ions out of the cell? What tends to draw them into the cell?

See page 34 for the answer.

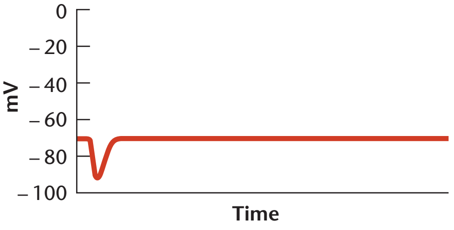
Why a Resting Potential?

The body invests much energy to operate the sodium–potassium pump that maintains the resting potential. Why is it worth so much energy? The resting potential prepares the neuron to respond rapidly. Excitation of the neuron opens sodium channels, letting sodium enter the cell rapidly. Because the membrane did its work in advance by keeping so much sodium outside, the cell is prepared to respond vigorously to a stimulus.

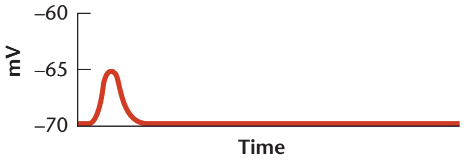
Compare the resting potential of a neuron to a poised bow and arrow: An archer who pulls the bow in advance and then waits is ready to fire at the appropriate moment. The neuron uses the same strategy. The resting potential remains stable until the neuron is stimulated.

The Action Potential

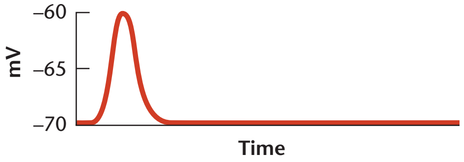
Axons send messages called **action potentials**. Let's begin by considering what happens when the resting potential is disturbed. When an axon's membrane is at rest, a microelectrode, as depicted in Figure 1.20, shows a negative potential inside the axon. If we now use a different electrode to increase the negative charge, we can produce **hyperpolarization**, which means increased polarization. When the stimulation ends, the charge returns to its original resting level. The recording looks like this:



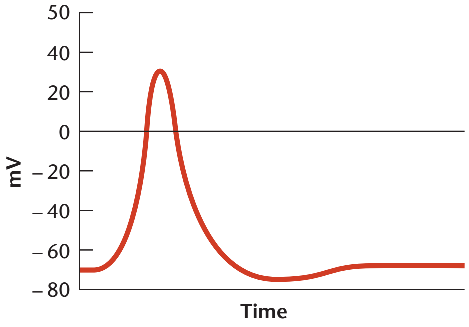
Now let's apply a brief current to **depolarize** the neuron—that is, reduce its polarization toward zero. If we apply a small depolarizing current, we get a result like this:



With a slightly stronger depolarizing current, the potential rises slightly higher but again returns to the resting level:



Now let's apply a still stronger current. When the potential reaches the **threshold**, the membrane opens its sodium channels and permits sodium ions to flow into the cell, driving the membrane potential upward, far beyond what the stimulus itself provided:



Any *subthreshold* stimulation produces a small response that quickly decays. Any stimulation beyond the threshold, regardless of how far beyond, produces a big response like the one depicted, known as the action potential. The peak of the action potential, shown as +30 mV in this illustration, varies from one axon to another, but it is consistent for a given axon.

Stop & Check

17. What is the difference between a hyperpolarization and a depolarization?
18. What happens if the depolarization does or does not reach the threshold?

See page 34 for the answer.

The All-or-None Law

Any depolarization that reaches or passes the threshold produces an action potential. For a given neuron, all action potentials are approximately equal in amplitude

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(intensity) and velocity. Slight variations occur spontaneously, but not because of the stimulus. More properly stated, the **all-or-none law** is that the amplitude and velocity of an action potential are independent of the intensity of the stimulus that initiated it, provided that the stimulus reaches the threshold. By analogy, imagine flushing a toilet: You need to press at least a certain strength (the threshold), but pressing harder does not make the toilet flush faster or more vigorously. Similarly, when you flick the switch to turn on the lights in your room, flicking the switch harder would not make the lights brighter.

The all-or-none law constrains how an axon can send a message. To signal the difference between a weak stimulus and a strong stimulus, all that an axon can change is the frequency of its action potentials, or their timing. By analogy, if you wanted to flick the lights in your room to send signals to someone outside, you could flick the switch frequently to mean one thing and flick it less often to mean something else. You could also flick the switch on and off at different rhythms.

> Flash-flash . . . [long pause] . . . flash-flash

might mean something different from

> Flash . . . [pause] . . . flash . . . [pause] . . . flash . . .
> [pause] . . . flash.

The nervous system uses both types of coding. For example, a taste axon shows one rhythm of responses for sweet tastes and a different rhythm for bitter tastes (Di Lorenzo et al., 2009).

Stop & Check

19. State the all-or-none law.
20. Does the all-or-none law apply to dendrites? Why or why not?

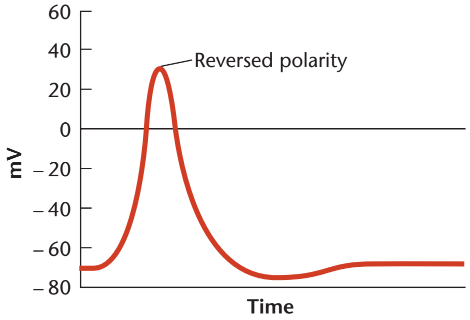
See page 34 for the answer.

The Molecular Basis of the Action Potential

The chemical events behind the action potential make sense if you remember three principles:

1. At the start, sodium ions are mostly outside the neuron, and potassium ions are mostly inside.
2. Depolarizing the membrane opens the sodium and potassium channels.
3. At the peak of the action potential, the sodium channels close.

Let's go through the process in more detail. A neuron's membrane contains cylindrical proteins, like the ones in Figure 1.19, with different sizes and shapes of openings. A protein that allows sodium to cross is a sodium channel (or gate), and one that lets potassium cross is a potassium channel. These are called **voltage-gated channels**, because they open or close depending on the voltage across the membrane. At the resting potential, the sodium channels are fully closed, and the potassium channels are almost fully closed. As the membrane becomes depolarized, both the types of channels begin to open, allowing freer flow. At first, opening the potassium channels makes little difference, but opening the sodium channels makes a big difference, because both the electrical gradient and the concentration gradient tend to drive sodium ions into the neuron. Sodium ions enter the cell rapidly, and the electrical potential across the membrane quickly passes beyond zero to a reversed polarity, as depicted in the following diagram:



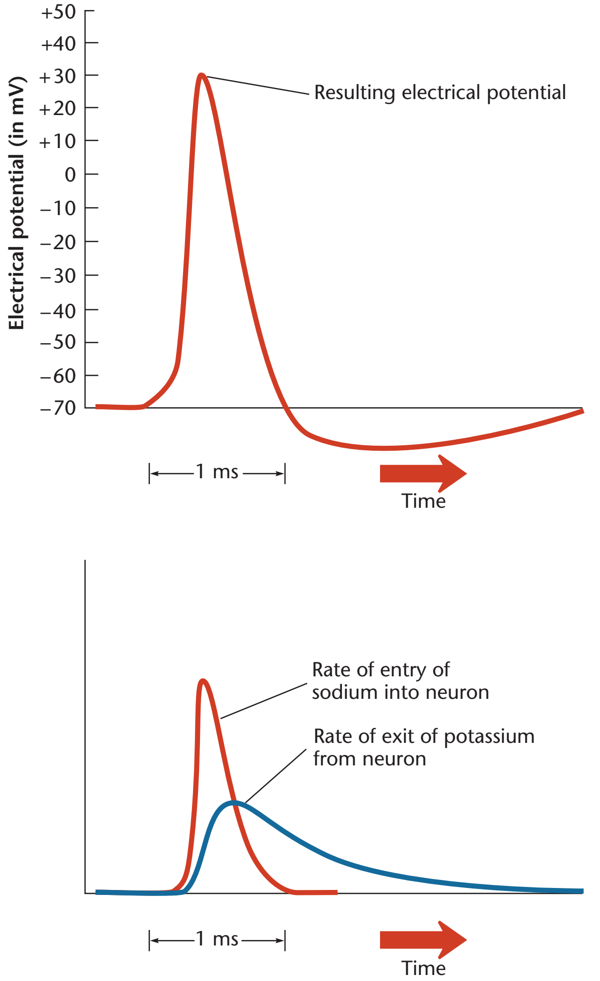
Of all the sodium ions near the axon, less than 1 percent cross the membrane during an action potential, and sodium ions remain far more concentrated outside than inside. Because of the concentration gradient, sodium ions would continue to enter the cell, except that the sodium gates snap shut at the peak of the action potential.

Then what happens? Remember that depolarizing the membrane also opens potassium channels. At first, opening those channels made little difference, but after so many sodium ions have crossed the membrane, the inside of the cell has a slight positive charge instead of its usual negative charge. At this point both the concentration gradient and the electrical gradient drive potassium ions out of the cell. Because the potassium channels remain open after the sodium channels close, enough potassium leaves to drive the membrane back to its original level and then slightly beyond it. Figure 1.23 summarizes the key movements of ions during an action potential.

At the end of this process, the membrane has returned to its resting potential, but the inside of the neuron has slightly more sodium ions and slightly fewer potassium ions than before. Eventually, the sodium–potassium pump restores the original distribution of ions, but that process takes time. After an unusually rapid series of action potentials, the pump cannot keep pace, and sodium accumulates in the axon, producing potentially toxic effects. However, excessive stimulation occurs only under abnormal conditions, such as during a stroke or after the use of certain drugs. Don't worry that thinking too hard will explode your brain cells.

Figure 1.23 The movement of sodium and potassium ions during an action potential

Sodium ions cross during the peak of the action potential, and potassium ions cross later in the opposite direction, returning the membrane to its original polarization.



Action potentials require the flow of sodium and potassium. **Local anesthetic** drugs, such as Novocain and Xylocaine, attach to the sodium channels of the membrane, preventing sodium ions from entering. When a dentist administers Novocain before drilling into one of your teeth, receptors in your teeth scream, "pain, pain, pain!" but the axons cannot transmit the message to your brain, and you don't feel it.

Stop & Check

21. During the rise of the action potential, do sodium ions move into the cell or out of it? Why?
22. As the membrane reaches the peak of the action potential, what brings the membrane down to the original resting potential?

See page 34 for the answer.

Propagation of the Action Potential

Now let's consider how the action potential moves down the axon. Remember, it is important for axons to convey impulses without any loss of strength over distance.

During an action potential, sodium ions enter the axon. Temporarily, the spot where they enter is positively charged in comparison with neighboring areas along the axon. The positive charge flows to neighboring regions of the axon, where they slightly depolarize the next area of the membrane, causing it to reach its threshold and open its sodium channels. The membrane regenerates the action potential at that point. In this manner, the action potential travels along the axon, as in Figure 1.24.

The term **propagation of the action potential** describes the transmission of an action potential down an axon, just as propagation of an animal species is the production of offspring. In a sense, the action potential gives birth to a new action potential at each point along the axon.

An action potential starts in an axon and propagates without loss from start to finish. However, at its start, it "back-propagates" into the cell body and dendrites (Lorincz and Nusser, 2010). The cell body and dendrites do not conduct action potentials, but they passively register the electrical event that started in the nearby axon. This back-propagation is important: When an action potential back-propagates into a dendrite, the dendrite becomes more susceptible to the structural changes responsible for learning.

Let's review the action potential:

- When an area of the axon membrane reaches its threshold, sodium channels and potassium channels open.
- Opening sodium channels lets sodium ions rush into the axon. At first, opening the potassium channels produces little effect.
- Positive charge flows down the axon and opens voltage-gated sodium channels at the next point.
- At the peak of the action potential, the sodium gates snap shut.
- Because voltage-gated potassium channels remain open, potassium ions flow out of the axon, returning the membrane toward its original depolarization.
- A few milliseconds later, the voltage-dependent potassium channels close.

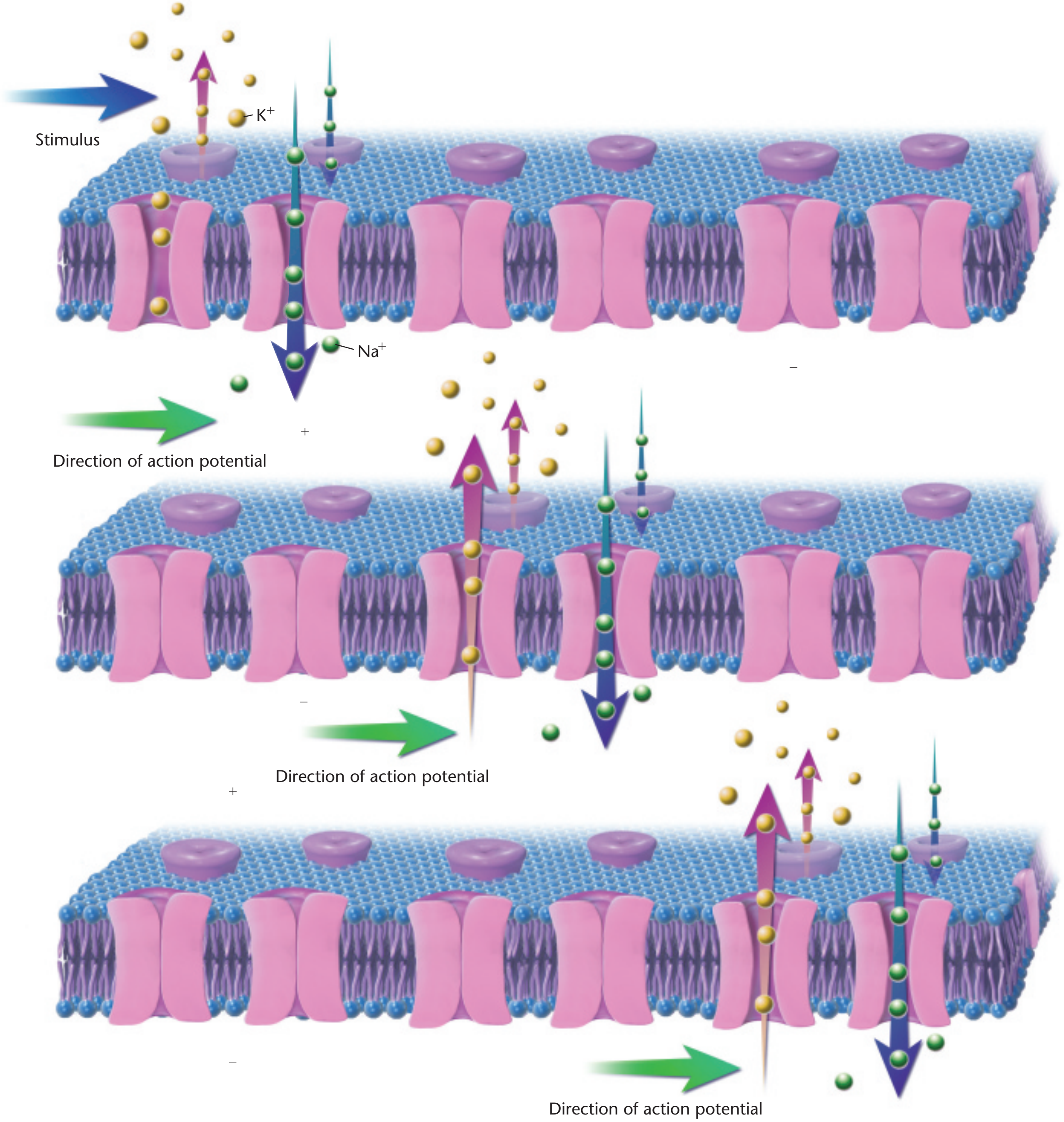
All of this may seem like a lot to memorize, but it is not. Everything follows logically from the facts that voltage-gated sodium and potassium channels open when the membrane is depolarized, and that sodium channels snap shut at the peak of the action potential.

The Refractory Period

When the action potential is at its peak, the electrical potential across the membrane is above the threshold. Why doesn't the cell produce another action potential during this

Figure 1.24 Propagation of an action potential

As an action potential occurs at one point on the axon, enough sodium enters to depolarize the next point to its threshold, producing an action potential at that point. The action potential flows along the axon, remaining at equal strength. Behind each area of sodium entry, potassium ions exit, restoring the resting potential.


Stimulus
K+
Na+
–
+
Direction of action potential
–
Direction of action potential
+
–
Direction of action potential

period? (If it did, the membrane would go into permanent depolarization.) The reason is that, at the peak of the action potential, the sodium channels shut tightly and remain tightly shut for approximately the next millisecond. This period is the **absolute refractory period**, the time when the membrane cannot produce an action potential, regardless of the stimulation. After that millisecond, the sodium channels relax a bit, but the rapid departure of potassium ions has driven the membrane potential farther into negative territory than usual. At that time, which lasts another

2 to 4 ms, the membrane is in a **relative refractory period**, when a stronger-than-usual stimulus is necessary to initiate an action potential. Thus, the **refractory period** depends on two facts: The sodium channels are closed, and potassium is flowing out of the cell.

Reexamine Figure 1.24 for a moment. As the action potential travels down the axon, what prevents the electrical charge from flowing backwards? Nothing. In fact, the electrical charge does flow in both directions. Then what prevents an action potential from reinvading the areas that it has just passed? The answer is that the areas it just passed are in their refractory period.

Stop & Check

23. Suppose researchers find that axon A can produce up to 1,000 action potentials per second (at least briefly, with maximum stimulation), but axon B can never produce more than 100 per second (regardless of the strength of the stimulus). What could we conclude about the refractory periods of the two axons?

See page 35 for the answer.

The Myelin Sheath and Saltatory Conduction

In the thinnest axons, action potentials travel at a velocity of less than 1 meter/second (m/s). Increasing the diameter brings conduction velocity up to about 10 m/s. At that speed, an impulse along an axon between a giraffe's spinal cord and its foot would take about half a second. To increase the speed still more, vertebrate axons evolved a special mechanism: sheaths of **myelin**, an insulating material composed of fats and proteins.

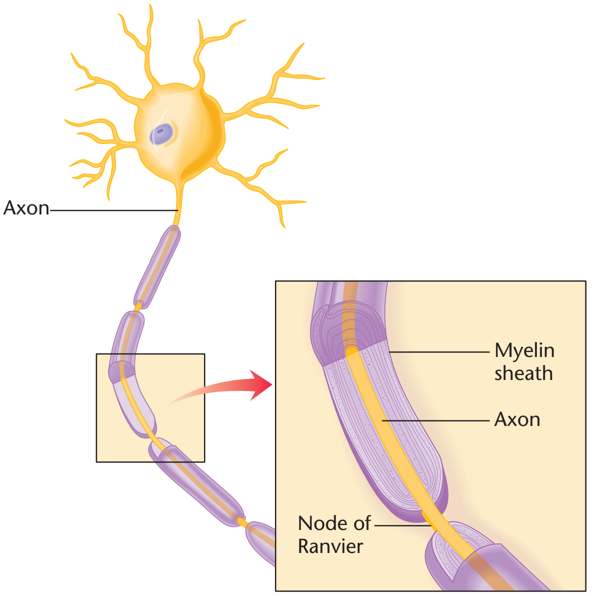
Consider the following analogy. Suppose your job is to take written messages over a long distance without using any mechanical device. Taking a message and running with it would reach the destination, but slowly. If you tied a message to a ball and threw it, you could increase the speed, but your throw would not travel far enough. The best solution would be to station people at moderate distances along the route and throw the message-bearing ball from person to person until it reaches its destination.

The same principle applies to **myelinated axons**, those covered with a myelin sheath. Myelinated axons, present only in vertebrates, are covered with layers of fats and proteins. The myelin sheath is interrupted periodically by short sections called nodes of Ranvier, each one about 1 micrometer wide, as shown in Figure 1.25. In myelinated axons, the action potential starts at the first node of Ranvier (Kuba et al., 2006).

Imagine an action potential at the first myelin segment. The action potential cannot regenerate along the membrane between nodes because the axon has few if any sodium channels between nodes (Catterall, 1984). After an action potential occurs at a node, sodium ions enter the axon and diffuse, pushing a chain of positive charge along the axon to the next node, where they quickly regenerate the action potential (Figure 1.26). The jumping of action potentials from node to node is referred to as **saltatory conduction**, from the Latin word *saltare*, meaning "to jump." (The same root shows up in the word *somersault.*) In addition to providing rapid conduction of impulses, saltatory conduction conserves energy: Instead of admitting sodium ions at every point along the axon and pumping them out, a myelinated axon admits sodium only at its nodes.

Figure 1.25 An axon surrounded by a myelin sheath and interrupted by nodes of Ranvier

The inset shows a cross-section through both the axon and the myelin sheath. The anatomy is distorted here to show several nodes; in fact, the distance between nodes is generally at least 100 times as long as a node.



Cutaway view of axon wrapped in myelin

In multiple sclerosis, the immune system attacks myelin sheaths. An axon that has lost its myelin is not the same as an axon that never had myelin, because the axon lacks sodium channels where the myelin used to be (Waxman and Ritchie, 1985). Consequently, most action potentials die out between one node and the next. Multiple sclerosis can produce visual impairments, poor muscle coordination, or other problems.

Stop & Check

24. In a myelinated axon, how would the action potential be affected if the nodes were much closer together? How might it be affected if the nodes were much farther apart?

See page 35 for the answer.

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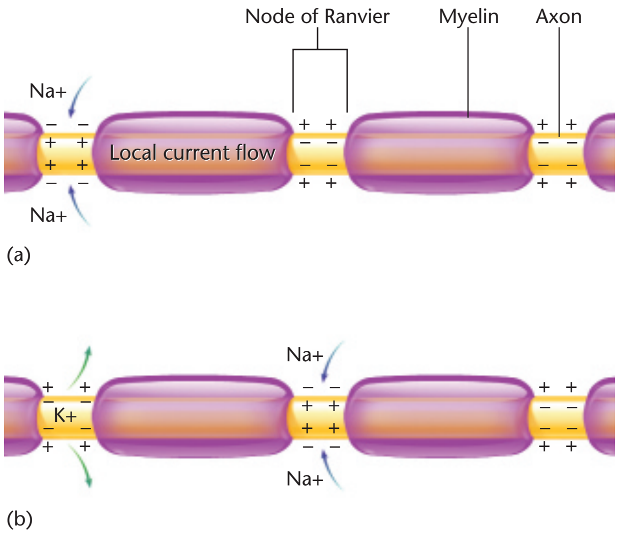
Figure 1.26 Saltatory conduction in a myelinated axon

An action potential at the node triggers flow of current to the next node, where the membrane regenerates the action potential. Myelin sheaths are much longer than depicted here, relative to the size of the nodes of Ranvier and the diameter of the axon.



Local Neurons

Many tiny neurons, called **local neurons**, have no axon and communicate only with their immediate neighbors. Because they have no axon, they do not produce action potentials, and they do not follow the all-or-none law. In such a cell, greater amounts of stimulation produce greater depolarization, called a **graded potential**, that spreads over the surface of the tiny neuron, declining in strength over distance. Most local neurons have inhibitory effects on neighboring cells.

Local neurons are difficult to study because it is almost impossible to insert an electrode into a tiny cell without damaging it. Most of our knowledge, therefore, comes from larger neurons, and that bias in our research methods may have led to a misconception. Many years ago, neuroscientists knew nothing about local neurons except that they were small, and some scientists assumed that the small neurons were immature. As one textbook author put it, "Many of these [neurons] are small and apparently undeveloped, as if they constituted a reserve stock not yet utilized in the individual's cerebral activity" (Woodworth, 1934, p. 194).

Possibly this misunderstanding was the origin of that widespread, nonsensical belief that "they say we use only 10 percent of our brain." (Who are "they," incidentally?) Other origins have also been suggested for this belief. No one is sure where it originated, but people have been quoting it to one another for more than a century—a remarkably persistent belief, given its total lack of justification. What does it mean? Does it mean that you could lose 90 percent of your brain and still behave normally? Good luck with that one. Perhaps it means that only 10 percent of your neurons are active at any given moment. Depending on how we define "given moment," 10 percent might or might not be correct, but in any case, it is irrelevant. If you could contract all your muscles at the same time, you would not be a great athlete. You would just have spasms. If you could activate all your neurons at one time, you would not have brilliant thoughts; you would have an epileptic seizure. Similarly, when you play a classical piano, at any moment you are using no more than 10 percent of its keys, but playing all 88 keys at once would not make great music. Meaningful thoughts and activities require activating some neurons and inhibiting others, and the inhibition is just as important as the excitation. You use all of your brain, regardless of how well you are using it.

Module 1.3 | In Closing

Neurons and Messages

What you have been reading about action potentials and sodium channels probably seems remote from most issues in psychology. But these physiological mechanisms are the building blocks that we need to understand before delving into synapses, the connections between neurons. Synapses, the decision makers of your brain, receive their input from axons. All experience originates from the chemical processes we have explored in this chapter.

Summary

1. The action potential transmits information without loss of intensity over distance. The cost is a delay between the stimulus and its arrival in the brain. **25**
2. The inside of a resting neuron has a negative charge with respect to the outside, mainly because of negatively charged proteins inside the neuron.

The sodium–potassium pump moves sodium ions out of the neuron, and potassium ions in. **25**

3. When the membrane is at rest, both the electrical gradient and the concentration gradient would drive sodium ions into the cell, except that its gates are closed. The electrical gradient tends to move potassium ions into the cell, but the concentration gradient tends to move it out. The two forces almost balance out, but not quite, leaving a slight tendency for potassium to exit the cell. **25**
4. The all-or-none law: For any stimulus greater than the threshold, the amplitude and velocity of the action potential are independent of the size of the stimulus that initiated it. **28**
5. When the membrane is depolarized enough to reach the cell's threshold, sodium and potassium channels open. Sodium ions enter rapidly, reducing and reversing the charge across the membrane. This event is known as the action potential. **29**
6. After the peak of the action potential, the membrane returns toward its original level of polarization because of the outflow of potassium ions. **29**
7. The action potential is regenerated at successive points along the axon as sodium ions flow through the core of the axon and stimulate the next point along the axon to its threshold. The action potential maintains a constant magnitude as it passes along the axon. **30**
8. Immediately after an action potential, the membrane enters a refractory period during which it is resistant to starting another action potential. **30**
9. In axons that are covered with myelin, action potentials form only in the nodes between myelinated segments. Transmission in myelinated axons is faster than in unmyelinated axons. **32**
10. Local neurons are small, with no axon. They convey information over short distances. **33**
11. Contrary to a popular belief, people use all of their brain, not some smaller percentage. **33**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

absolute refractory period **30**
action potential **28**
all-or-none law **28**
concentration gradient **27**
depolarize **28**
electrical gradient **25**
graded potentials **33**
hyperpolarization **28**
local anesthetic **29**
local neurons **33**
myelin **32**
myelinated axons **32**
polarization **25**
propagation of the action potential **30**
refractory period **31**
relative refractory period **30**
resting potential **26**
saltatory conduction **32**
selectively permeable **26**
sodium–potassium pump **26**
threshold **28**
voltage-gated channels **29**

Thought Questions

1. Suppose the threshold of a neuron were the same as the neuron's resting potential. What would happen? At what frequency would the cell produce action potentials?
2. In the laboratory, researchers can apply an electrical stimulus at any point along the axon, making action potentials travel in both directions from the point of stimulation. An action potential moving in the usual direction, away from the cell body, travels in the *orthodromic* direction. An action potential traveling toward the cell body travels in the *antidromic* direction. If we started an orthodromic action potential at the start of the axon and an antidromic action potential at the opposite end of the axon, what would happen when they met at the center? Why?
3. If a drug partly blocks a membrane's potassium channels, how does it affect the action potential?

Stop & Check Answers

15. Sodium ions are more concentrated outside the cell, and potassium is more concentrated inside.
16. When the membrane is at rest, the concentration gradient tends to drive potassium ions out of the cell, and the electrical gradient draws them into the cell. The sodium–potassium pump also draws them into the cell.
17. A hyperpolarization is an exaggeration of the usual negative charge within a cell, making it more negative level than usual. A depolarization is a decrease in the amount of negative charge within the cell.
18. If the depolarization reaches or passes the threshold, the cell produces an action potential. If it is less than threshold, no action potential arises.

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19. According to the all-or-none law, for a given axon, every depolarization beyond the threshold produces an action potential of about the same amplitude and velocity.

20. The all-or-none law does not apply to dendrites, because they do not have action potentials.

21. During the action potential, sodium ions move into the cell. The voltage-dependent sodium gates have opened, letting sodium move freely. Sodium is attracted to the inside of the cell by both an electrical and a concentration gradient.

22. After the peak of the action potential, potassium ions exit the cell, driving the membrane back to the resting potential. Important note: The sodium–potassium pump is too slow for this purpose.

23. Axon A must have a shorter absolute refractory period, about 1 ms, whereas B has a longer absolute refractory period, about 10 ms.

24. If the nodes were closer, the action potential would travel more slowly. If they were much farther apart, the current might not be able to stimulate the next node enough to reach its threshold.

Module 1.3 | End-of-Module Quiz

1. Why is an action potential a better way for an axon to transmit information than electrical conduction would be?

- **a.** An action potential can convey information to a greater number of cells.
- **b.** An action potential conveys information more rapidly.
- **c.** An action potential travels both directions along an axon.
- **d.** An action potential does not decrease its intensity over distance.

2. When the membrane is at rest, where are the sodium and potassium ions, mostly?

- **a.** Sodium is mostly outside the cell, and potassium is mostly inside.
- **b.** Sodium is mostly inside the cell, and potassium is mostly outside.
- **c.** Both are mostly outside the cell.
- **d.** Both are mostly inside the cell.

3. What does the sodium-potassium pump do?

- **a.** It pumps sodium into the cell, and potassium out of the cell.
- **b.** It pumps sodium out of the cell, and potassium into the cell.
- **c.** It pumps both sodium and potassium out of the cell.
- **d.** It pumps both sodium and potassium along the axon, in the same direction as the action potential.

4. When the membrane is at rest, which gradient or gradients tend to draw sodium ions into the cell?

- **a.** The electrical gradient
- **b.** The concentration gradient
- **c.** Neither the electrical gradient nor the concentration gradient
- **d.** Both the electrical gradient and the concentration gradient

5. When the membrane is at rest, which gradient or gradients tend to draw potassium ions out of the cell?

- **a.** The electrical gradient
- **b.** The concentration gradient
- **c.** Neither the electrical gradient nor the concentration gradient
- **d.** Both the electrical gradient and the concentration gradient

6. What causes the rising portion of the action potential?

- **a.** Sodium ions are moving out of the cell.
- **b.** Sodium ions are moving into the cell.
- **c.** Both sodium and potassium ions are moving out of the cell.
- **d.** Potassium ions are moving into the cell.

7. After the peak of the action potential, the membrane returns toward its resting level. What accounts for this recovery?

- **a.** The sodium–potassium pump removes the extra sodium.
- **b.** Sodium ions move out because of the electrical gradient.
- **c.** Potassium ions move out because of the concentration gradient.
- **d.** Potassium ions move in because of the concentration gradient.

8. If a membrane is depolarized to twice its threshold, what happens?

- **a.** The action potential is twice as strong as usual.
- **b.** The action potential travels twice as fast as usual.
- **c.** The action potential is slightly stronger and slightly faster than usual.
- **d.** The action potential is the same as usual.

9. The all-or-none law applies to what part of a neuron?

- **a.** The cell body
- **b.** The axon
- **c.** The dendrites
- **d.** The mitochondria

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10. What causes the absolute refractory period of an axon?

a. The sodium channels are shut.
b. The potassium channels are shut.
c. The potassium channels are open.
d. The sodium-potassium pump has stopped.

11. What does the myelin sheath of an axon accomplish?

a. It facilitates communication among axons.
b. It enables action potentials to travel both directions along an axon.
c. It increases the velocity of action potentials.
d. It stores nutrients for the axon.

12. How do local neurons differ from other neurons?

a. They do not have axons.
b. They do not have mitochondria.
c. They connect only with glia, not with other neurons.
d. They move from one brain area to another.

13. About what percentage of the brain does an average person use?

a. 10 percent
b. 30 percent
c. 50 percent
d. 100 percent

Answers: 1d, 2a, 3b, 4d, 5b, 6b, 7c, 8d, 9b, 10a, 11c, 12a, 13d.

Suggestions for Further Reading

Ascoli, G. A. (2015). *Trees of the brain, roots of the mind.* Cambridge, MA: MIT Press. A richly illustrated description of axons, dendrites, and what they have to do with psychology.

Morrison, A. R. (2009). *An odyssey with animals: A veterinarian's reflections on the animal rights & welfare debate.* New York: Oxford University Press. A defense of animal research that acknowledges the difficulties of the issue and the competing values at stake.

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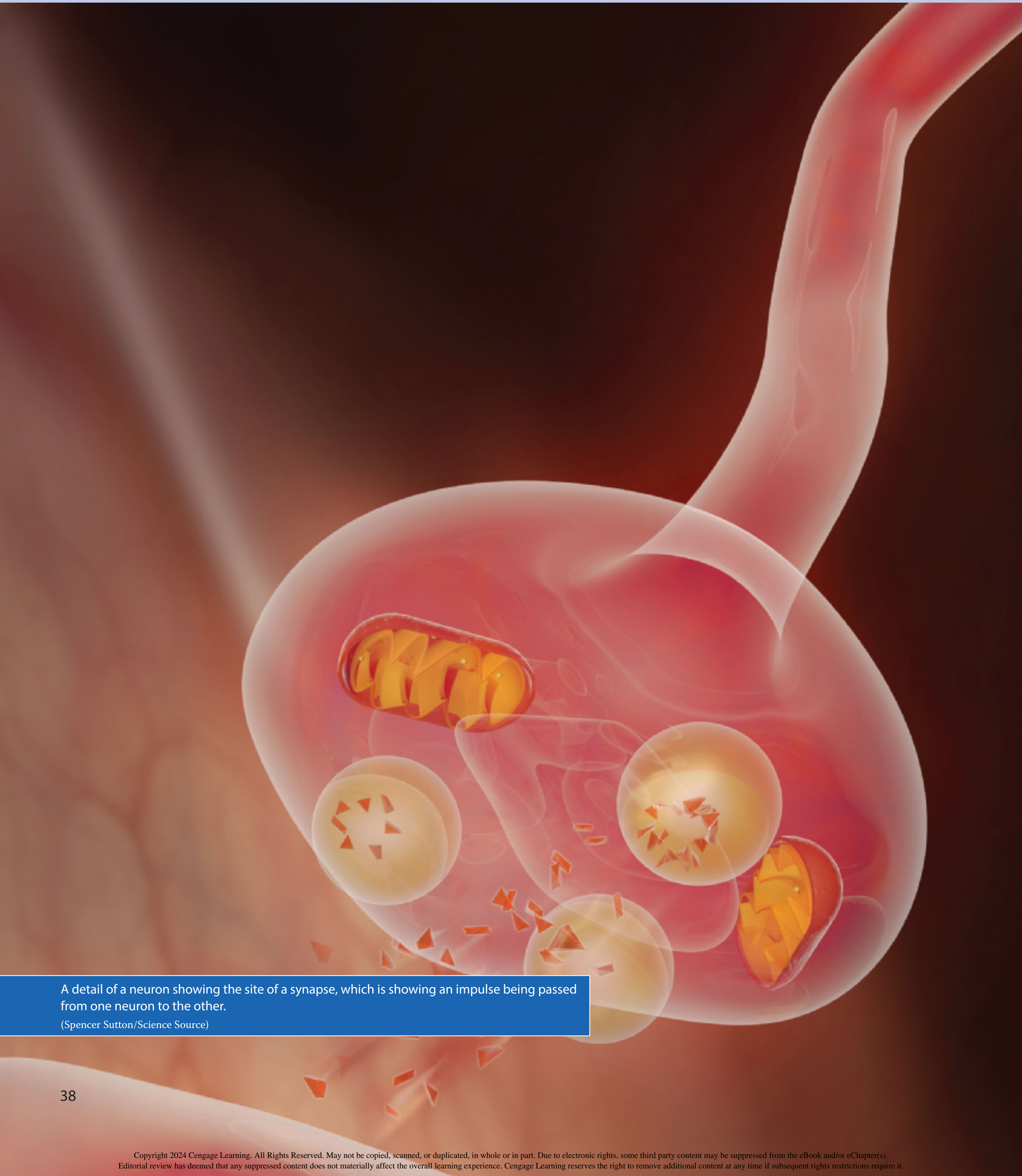
Chapter 2



A detail of a neuron showing the site of a synapse, which is showing an impulse being passed from one neuron to the other.

(Spencer Sutton/Science Source)

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Synapses

Chapter Outline

Module 2.1

The Concept of the Synapse

The Properties of Synapses

Relationship among EPSP, IPSP, and Action Potentials

In Closing: The Neuron as Decision Maker

Module 2.2

Chemical Events at the Synapse

The Discovery of Chemical Transmission at Synapses

The Chemical Events at a Synapse

Hormones

In Closing: Neurotransmitters and Behavior

Learning Objectives

After studying this chapter, you should be able to:

1. Describe how Charles Sherrington used behavioral observations to infer the major properties of synapses.
2. Explain how EPSPs and IPSPs produce temporal and spatial summation.
3. Discuss the importance of inhibition in the nervous system.
4. List and explain the sequence of events at a synapse, from synthesis of neurotransmitters, through stimulation of receptors, to the disposition of the transmitter molecules.
5. Distinguish between ionotropic and metabotropic receptors and explain how each of them works.
6. Discuss how certain drugs affect behavior by their effects at synapses.
7. List some hormones and their effects.

If you had to communicate with someone without sight or sound, what would you do? Chances are, you would try to devise a touch code or a system of electrical impulses. You might not think of passing chemicals back and forth. Chemicals are, however, the main way your neurons communicate, at specialized junctions called *synapses*.

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Module 2.1

The Concept of the Synapse

Learning Objectives

After studying this module, you should be able to:

1. Describe how Charles Sherrington used behavioral observations to infer the major properties of synapses.
2. Explain how EPSPs and IPSPs produce temporal and spatial summation.
3. Discuss the importance of inhibition in the nervous system.

Around the time when Santiago Ramón y Cajal anatomically demonstrated a narrow gap separating one neuron from another, Charles Scott Sherrington (1906) physiologically demonstrated that neurons communicate at a junction between them, the **synapse**. Ramon y Cajal and Sherrington are regarded as the great pioneers of modern neuroscience, and their nearly simultaneous discoveries supported each other: If communication between neurons is special in some way, then there can be no doubt that neurons are anatomically separate from one another. Sherrington's discovery was an amazing feat of scientific reasoning, as he used behavioral observations to infer the properties of synapses half a century before researchers had the technology to measure those properties directly.

Properties of Synapses

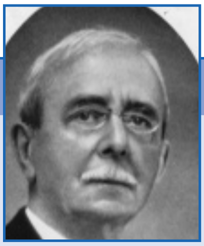
Sherrington based his conclusions on studies of **reflexes**, automatic muscular responses to stimuli. In a leg flexion reflex, a sensory neuron excites a second neuron, which in turn excites a motor neuron, which excites a muscle, as in Figure 2.1. The circuit from sensory neuron to muscle response is a **reflex arc**. If neurons are separate from one another, as Ramon y Cajal had demonstrated, a reflex must require communication between neurons, and therefore, measurements of reflexes might reveal the properties of their communication.

Sherrington strapped a dog into a harness and pinched one of the dog's feet. After a fraction of a second, the dog *flexed* (raised) the pinched leg and *extended* the other legs. Sherrington found the same reflexive movements after he made a cut that disconnected the spinal cord from the brain. Evidently, the spinal cord controlled the flexion and extension reflexes. In fact, the movements were more consistent after he separated the spinal cord from the brain. In an intact animal, messages descending from the brain modify the reflexes, making them stronger at some times and weaker at others.

Sherrington observed several properties of reflexes that suggest special processes at the junctions between neurons: (1) Reflexes are slower than conduction along an axon. (2) Several weak stimuli presented at nearby places or times combine their effects. (3) When one set of muscles becomes excited, a different set becomes relaxed. Let's consider each of these points and their implications.

Speed of a Reflex and Delayed Transmission at the Synapse

When Sherrington pinched a dog's foot, the dog flexed that leg after a short delay. During the delay, an impulse had to travel up an axon from the skin receptor to the spinal cord, and then an impulse had to travel back down the leg to a muscle. Sherrington measured the distance that the impulse traveled from skin to spinal cord to muscle, and then he calculated the speed at which the impulse traveled. He found that the speed of conduction through the reflex arc varied

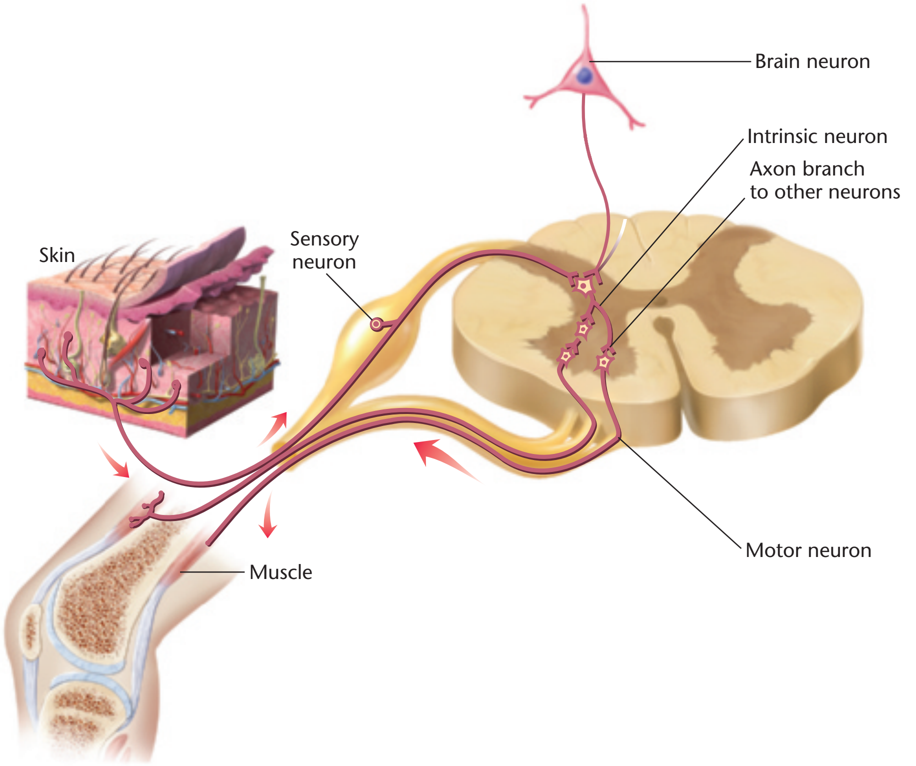

Hulton Archive/Getty Images

Charles Scott Sherrington (1857–1952)

A rainbow every morning who would pause to look at? The wonderful which comes often or is plentifully about us is soon taken for granted. That is practical enough. It allows us to get on with life. But it may stultify if it cannot on occasion be thrown off. To recapture now and then childhood's wonders is to secure a driving force for occasional grown-up thoughts. (Sherrington, 1941, p. 104)

Figure 2.1 A reflex arc for leg flexion

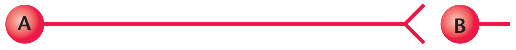
The anatomy has been simplified to show the relationship among sensory neuron, intrinsic neuron, and motor neuron.



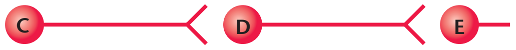
but was never more than about 15 meters per second (m/s). In contrast, previous research had measured action potential velocities along sensory or motor nerves at about 40 m/s. Sherrington concluded that some process must be slowing conduction through the reflex, and he inferred that the delay occurs where one neuron communicates with another (Figure 2.2). This idea established the existence of synapses. Sherrington, in fact, introduced the term *synapse.*

Figure 2.2 Sherrington's evidence for synaptic delay

An impulse traveling through a synapse in the spinal cord is slower than one traveling a similar distance along an uninterrupted axon.



The speed of conduction along an axon is about 40 m/s.



The speed of conduction through a reflex arc is slower and more variable, sometimes 15 m/s or less. Presumably, the delay occurs at the synapse.

Stop & Check

1. What evidence led Sherrington to conclude that transmission at a synapse is not the same as transmission along an axon?

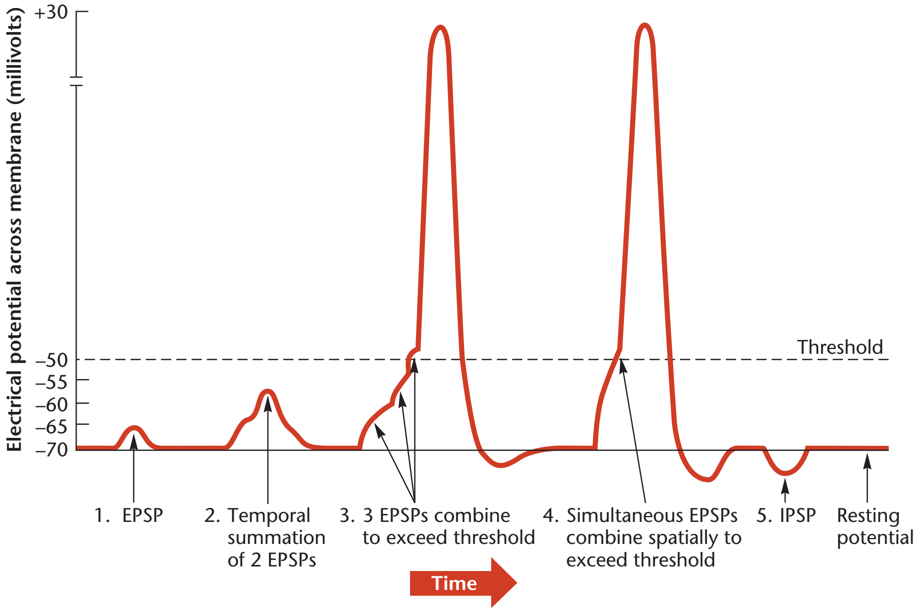
See page 46 for the answer.

Temporal Summation

Sherrington found that repeated stimuli within a brief time combine their effects. He called this phenomenon **temporal summation**, meaning summation over time. A light pinch of the dog's foot did not evoke a reflex, but a few rapidly repeated pinches did. The neuron delivering transmission is the **presynaptic neuron**, and the one receiving it is the **postsynaptic neuron**. Sherrington proposed that although a single subthreshold excitation in the postsynaptic neuron decays over time, it combines with a second excitation that follows quickly. With a rapid succession of pinches, each adds its effect to what remained from the previous ones, until the combination exceeds the threshold of the postsynaptic neuron, producing an action potential.

Decades later, Sherrington's former student, John Eccles (1964), attached microelectrodes to stimulate axons of presynaptic neurons while he recorded from the

Figure 2.3 Recordings from a postsynaptic neuron during synaptic activation



postsynaptic neuron. Depending on the charge he delivered through the microelectrode, Eccles recorded a slight depolarization of the membrane of the postsynaptic cell (point 1 in Figure 2.3) or a slight hyperpolarization (point 5).

What he produced was a graded potential. Unlike action potentials, which are always depolarizations, graded potentials may be either depolarizations (excitatory) or hyperpolarizations (inhibitory), and they decay over both time and distance. A graded depolarization is an **excitatory postsynaptic potential (EPSP)**, which results from a sodium ions entering the neuron. A graded hyperpolarization is an **inhibitory postsynaptic potential (IPSP)**, produced by flow of negatively charged chloride ions into the cell.

When Eccles produced two EPSPs within a short time, the second EPSP added to what was left of the first one (point 2 in Figure 2.3), producing temporal summation. At point 3 in Figure 2.3, a quick sequence of EPSPs combines to exceed the threshold and produce an action potential.

Spatial Summation

Sherrington also found that synapses have the property of **spatial summation**—summation over space. He again began with a pinch too weak to elicit a reflex. This time, instead of pinching one point twice, he pinched two points at once. Although neither pinch alone produced a reflex, together they did. Sherrington concluded that pinching two points activated sensory neurons whose axons converged onto a neuron in the spinal cord. Excitation from either sensory axon excited that spinal neuron, and a combination of excitations exceeded the threshold to produce an action potential (point 4 in Figure 2.3). Again, Eccles confirmed Sherrington's inference, demonstrating that EPSPs from several axons summate their effects on a postsynaptic cell (Figure 2.4). Temporal summation and spatial summation occur together when a neuron receives input from several axons in succession.

Stop & Check

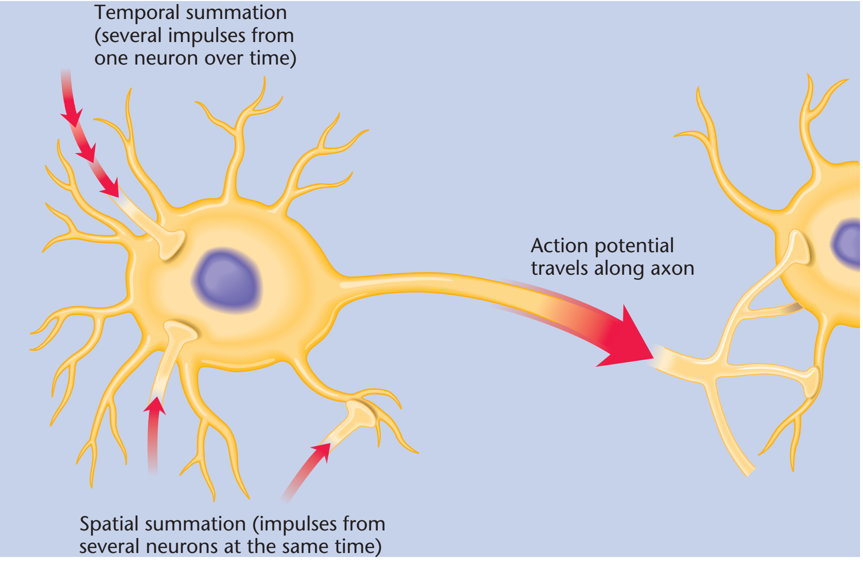
2. How does temporal summation differ from spatial summation?
3. What ion gates in the membrane open during an EPSP? What gates open during an IPSP?

See page 46 for the answer.

Inhibitory Synapses

When Sherrington vigorously pinched a dog's foot, the flexor muscles of that leg contracted, and so did the extensor muscles of the other three legs (Figure 2.5). You can find the value of this arrangement. A dog raising one leg needs to extend the other legs to maintain balance. The dog also relaxed the extensor muscles of the stimulated leg and the flexor muscles of the other legs. Sherrington's explanation assumed certain connections in the spinal cord: A pinch on the foot sends a message along a sensory neuron to an interneuron in the spinal cord that excites the motor neurons connected to the flexor

Figure 2.4 Temporal and spatial summation


Temporal summation (several impulses from one neuron over time)
Action potential travels along axon
Spatial summation (impulses from several neurons at the same time)

muscles of that leg and the extensor muscles of the other legs (Figure 2.6). The interneuron also sends messages to inhibit the extensor muscles in that leg and the flexor muscles of the three other legs.

Later researchers physiologically demonstrated those inhibitory synapses. At these synapses, input from an axon hyperpolarizes the postsynaptic cell, moving the cell's charge farther from the threshold and decreasing the probability of an action potential (point 5 in Figure 2.3).

Most neurons have a **spontaneous firing rate**, a periodic production of action potentials even without synaptic input. In such cases, the EPSPs increase the frequency of action potentials above the spontaneous rate, whereas IPSPs decrease it. For a neuron with a spontaneous firing rate of 10 action potentials per second, a stream of EPSPs might increase the rate to 15 or more, whereas a preponderance of IPSPs might decrease it to 5 or fewer. The spontaneous firing rate varies enormously

Figure 2.5 Antagonistic muscles

Flexor muscles draw an extremity toward the trunk of the body, whereas extensor muscles move an extremity away from the body.

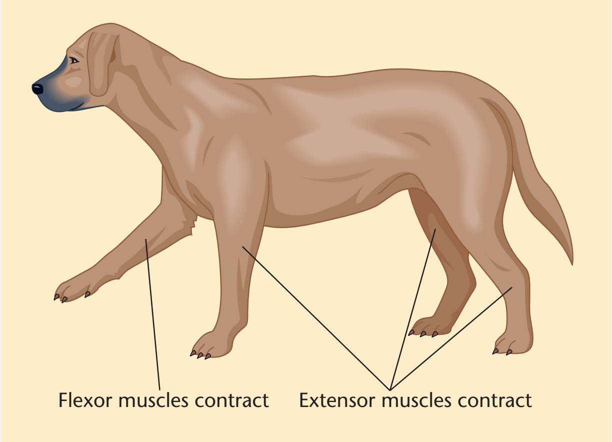
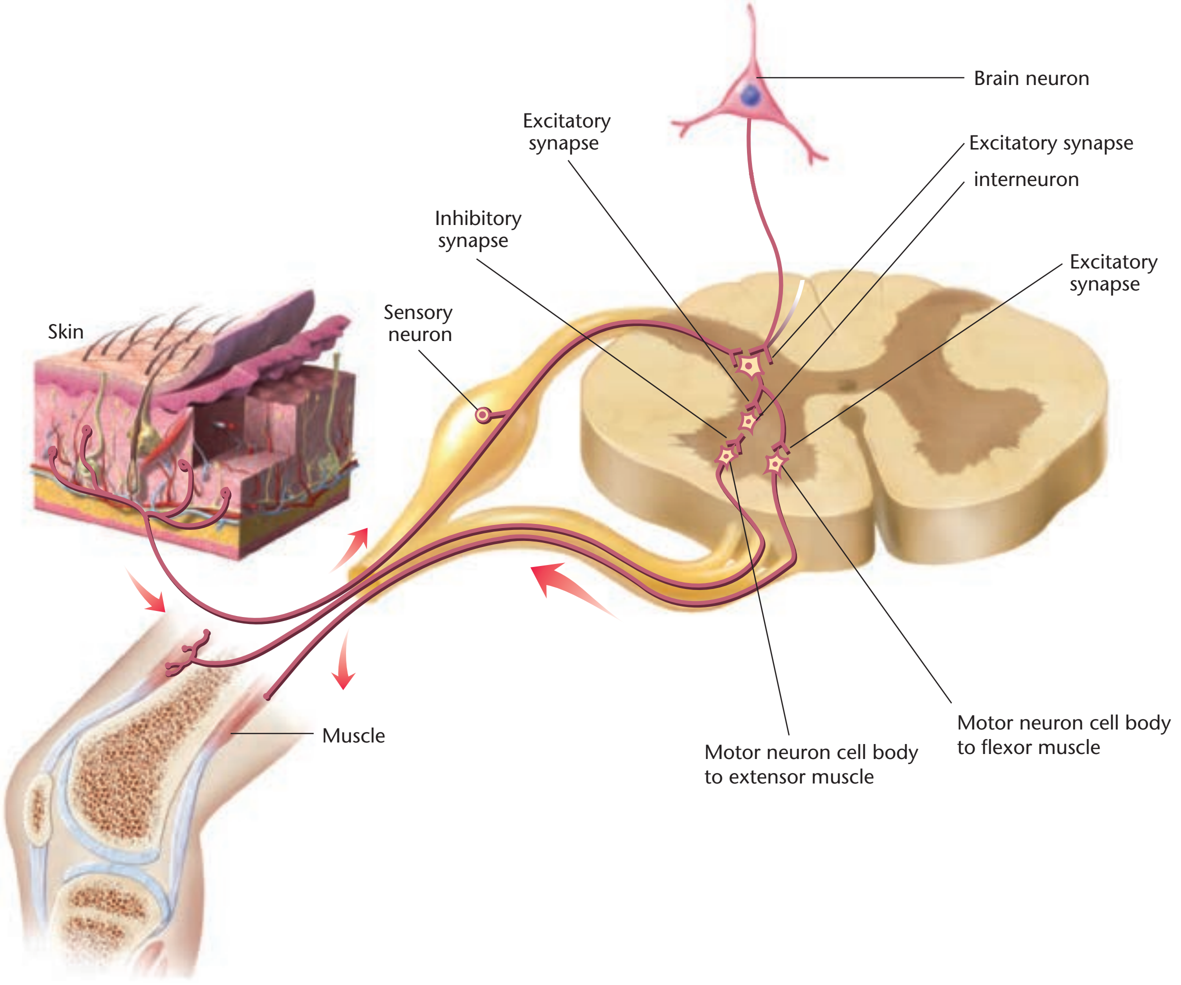

Flexor muscles contract
Extensor muscles contract

Figure 2.6 Sherrington's inferences of inhibitory synapses

When a flexor muscle is excited, input to the extensor muscle is inhibited. Sherrington inferred that the interneuron that excited a motor neuron to the flexor muscle also inhibited a motor neuron connected to the extensor muscle. Not depicted here are the connections to motor neurons controlling the other three legs.


Brain neuron
Excitatory synapse
Excitatory synapse
interneuron
Inhibitory synapse
Excitatory synapse
Skin
Sensory neuron
Muscle
Motor neuron cell body to extensor muscle
Motor neuron cell body to flexor muscle

among neurons, but for a given neuron, it stays within a narrow range (Trojanowski et al., 2021).

Today, we take for granted the concept of inhibition, but at Sherrington's time, the idea was controversial, as no one could imagine a mechanism to accomplish it. Establishing the idea of inhibition was critical not just for neuroscience but for psychology as well. Whenever we talk about inhibiting an impulse, we use a concept first demonstrated by Sherrington.

Stop & Check

4. What was Sherrington's evidence for inhibition in the nervous system?
5. Can an inhibitory message flow along an axon?

See page 46 for the answer.

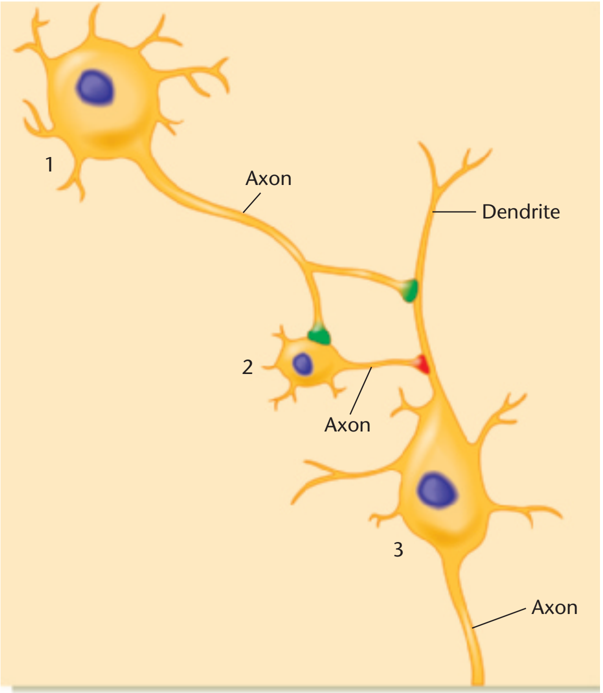
Relationship among EPSP, IPSP, and Action Potentials

Sherrington's work opened the way to exploring the wiring diagram of the nervous system. Consider the neurons depicted in Figure 2.7. When neuron 1 excites neuron 3, it also excites neuron 2, which inhibits neuron 3. The excitatory message reaches neuron 3 faster because it goes through just one synapse instead of two. The result is a burst of excitation (EPSP) in neuron 3, which quickly slows or stops. You can now understand how inhibitory messages can regulate the timing of activity.

For another wiring diagram, consider Figure 2.8. The axon from either cell A or cell B stimulates cell X with +1 unit. If the threshold of cell X is +1, then cell X responds to "A or B." If the threshold is +2, then cell X responds to

Figure 2.7 A possible wiring diagram for synapses

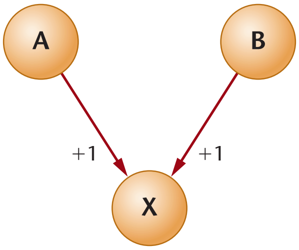
Excitatory synapses are in green, and inhibitory synapses are in red. In the circuit depicted here, excitation reaches the dendrite before inhibition. (Remember, any transmission through a synapse produces a delay.) The result is brief excitation of the dendrite.



(Based on Kullmann and Lamsa, 2007)

Figure 2.8 A simple wiring diagram for neurons

Neuron X could indicate "A or B" if its threshold is 1, and it could indicate "A and B" if its threshold is 2.



"A and B." Following this same logic, you may be able to imagine other constructions. Many mathematical models of the nervous system are based on connections like these. However, some synapses produce fast, brief effects, and others produce slow, long-lasting effects. Some synapses are larger than others and produce bigger effects (Holler et al., 2021). The effect of two synapses at the same time can be more than double the effect of either one, or less than double (Silver, 2010). Certain combinations of synapses summate more strongly than others do (Lavzin et al., 2012). Also, many neurons in the brain change their properties from one context to another. We need to go beyond simple wiring diagrams to explain cognitive functions (Barack and Krakauer, 2021).

Module 2.1 | In Closing

The Neuron as Decision Maker

The EPSPs and IPSPs reaching a neuron at a given moment compete with one another. The combined effect of EPSPs and IPSPs determines whether or not the postsynaptic cell fires an action potential. However, do not imagine that any single neuron decides what you will eat for breakfast. Complex behaviors depend on the contributions from a huge network of neurons.

Summary

1. The synapse is the point of communication between neurons. Charles Sherrington's observations of reflexes enabled him to infer the existence of synapses and many of their properties. **40**
2. Because transmission through a reflex arc is slower than transmission through an equivalent length of axon, Sherrington concluded that a process at the synapse delays transmission. **40**
3. Graded potentials (EPSPs and IPSPs) summate their effects. The summation of graded potentials from stimuli at different times is temporal summation. The summation of potentials from different locations is spatial summation. **41**
4. Inhibition is more than the absence of excitation. It is an active brake that suppresses excitation. For effective functioning of the nervous system, inhibition is just as important as excitation. **42**

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5. Stimulation at a synapse produces a brief graded potential in the postsynaptic cell. An excitatory graded potential (depolarization) is an EPSP. An inhibitory graded potential (hyperpolarization) is an IPSP. **42**
6. The balance between EPSPs and IPSPs determines the neuron's frequency of action potentials. **44**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

excitatory postsynaptic potential (EPSP)	**42**
inhibitory postsynaptic potential (IPSP)	**42**
postsynaptic neuron	**41**
presynaptic neuron	**41**
reflex arc	**40**
reflexes	**40**
spatial summation	**42**
spontaneous firing rate	**43**
synapse	**40**
temporal summation	**41**

Thought Questions

1. When Sherrington measured the reaction time of a reflex (i.e., the delay between stimulus and response), he found that the response occurred faster after a strong stimulus than after a weak one. Can you explain this finding? Remember that all action potentials—whether produced by strong or weak stimuli—travel at the same speed along a given axon.
2. Suppose neuron X has a synapse onto neuron Y, which has a synapse onto Z. Presume that no other neurons or synapses are present. An experimenter finds that stimulating neuron X causes an action potential in neuron Z after a short delay. However, she determines that the synapse of X onto Y is inhibitory. Explain how the stimulation of X might produce excitation of Z.
3. Figure 2.9 shows synaptic connections to produce a cell that responds to "A or B" or "A and B." Construct a diagram for a cell that responds to "A and B if not C."
4. Construct a wiring diagram for a cell that responds to "A *or* B if not C." This is trickier than it sounds. If you simply shift the threshold of cell X to 1, it will respond to "A if not C, or B if not C, or A and B even if C." Can you get X to respond to either A or B, but only if C is inactive? (Hint: You might need to introduce additional neurons.)

Stop & Check Answers

1. The velocity of conduction through a reflex arc is slower than the velocity of an action potential along an axon. Therefore, a delay must occur at the junction between one neuron and the next.
2. Temporal summation is the combined effect of quickly repeated stimulation at a single synapse. Spatial summation is the combined effect of several nearly simultaneous stimulations at several synapses onto one neuron.
3. During an EPSP, sodium gates open. During an IPSP, chloride gates open.
4. A reflex that stimulates a flexor muscle prevents contraction of the extensor muscles of the same limb. Sherrington inferred that an interneuron that excites one set of motor neurons inhibits the input to another set.
5. No. Only action potentials propagate along an axon. Inhibitory messages—IPSPs—decay over time and distance.

Module 2.1 | End-of-Module Quiz

1. In what way did Sherrington's conclusions agree with Ramón y Cajal's conclusions?
   - **a.** Both concluded that excitation competes with inhibition.
   - **b.** Both concluded that sodium and potassium are the key ions for transmission.
   - **c.** Both concluded that most behavior depends on unconscious influences.
   - **d.** Both concluded that neurons are separate from one another.

2. Sherrington based his conclusions on what type of evidence?
   - **a.** Microscopic examination of synapses
   - **b.** Results of injecting drugs into the spinal cord
   - **c.** Electrical recordings from inside neurons
   - **d.** Observations of reflexive responses

3. Why did Sherrington conclude that synaptic transmission differs from conduction along an axon?
   - **a.** Reflexes are slower than axonal transmission.
   - **b.** Certain chemicals can excite or inhibit synapses.
   - **c.** He was able to measure the electrical responses of the postsynaptic neurons.
   - **d.** He examined the synapses in an electron microscope.

4. An EPSP is an abbreviation for what?
   - **a.** Excitatory PostSynaptic Potential
   - **b.** Extra Possibility for Synaptic Potentiation
   - **c.** Exhibit of ParaSympathetic Progress
   - **d.** Error of Potential Synaptic Progression

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5. Although one pinch did not cause a dog to flex its leg, a rapid sequence of pinches did. Sherrington cited this observation as evidence for what?

- **a.** Temporal summation
- **b.** Spatial summation
- **c.** Inhibitory synapses
- **d.** Refractory period

6. The extensor muscles of a leg relax when the flexor muscles contract. Sherrington saw this observation as evidence for what?

- **a.** Voluntary control by the cerebral cortex
- **b.** More than one type of neurotransmitter chemical
- **c.** Inhibitory synapses
- **d.** Lamarckian evolution

7. What channels in a neuron open during an EPSP?

- **a.** Chloride
- **b.** Potassium
- **c.** Sodium
- **d.** Calcium

8. In what way were Sherrington's conclusions important for psychology as well as neuroscience?

- **a.** He demonstrated the importance of unconscious motivations.
- **b.** He demonstrated the importance of inhibition.
- **c.** He demonstrated the phenomenon of classical conditioning.
- **d.** He demonstrated the evolution of intelligence.

Answers: 1d, 2d, 3a, 4a, 5a, 6c, 7c, 8b.

Module 2.2

Chemical Events at the Synapse

Learning Objectives

After studying this module, you should be able to:

4. List and explain the sequence of events at a synapse, from synthesis of neurotransmitters, through stimulation of receptors, to the disposition of the transmitter molecules.
5. Distinguish between ionotropic and metabotropic receptors and explain how each of them works.
6. Discuss how certain drugs affect behavior by their effects at synapses.
7. List some hormones and their effects.

Although Charles Sherrington accurately inferred many properties of the synapse, he was wrong about one important point. Although he demonstrated that synaptic transmission was slower than transmission along an axon, he thought it was still too fast to depend on a chemical process, and he therefore concluded that it must be electrical. We now know that the great majority of synapses rely on chemical processes, which are much faster and more versatile than Sherrington or anyone else of his era would have guessed. Over the years, our understanding of synaptic activity has grown in many ways.

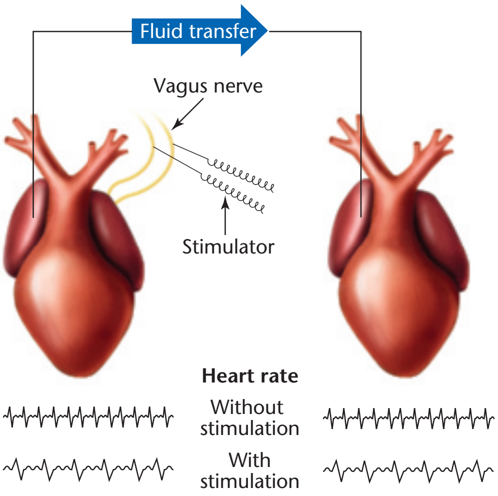
The Discovery of Chemical Transmission at Synapses

A set of nerves called the sympathetic nervous system accelerates the heartbeat, dilates the pupils of the eyes, and regulates other organs. T. R. Elliott (1905) reported that applying the hormone *adrenaline* directly to the surface of the heart, the stomach, or the pupils produces the same effects as the sympathetic nervous system. Elliott therefore suggested that the sympathetic nerves stimulate muscles by releasing adrenaline or a similar chemical.

However, this evidence was not decisive. Possibly adrenaline just mimicked effects of an electrical process. Sherrington's prestige was so great that most scientists ignored Elliott's results and continued to assume that synapses transmitted electrical impulses. Otto Loewi, a German physiologist, liked the idea of chemical synapses but did not determine how to demonstrate it more conclusively. In 1920, he awakened one night with an idea about what research to do. He wrote himself a note and went back to sleep. Unfortunately, the next morning he could not read his note! After feeling discouraged all day, he awoke the following night at 3 A.M. with the same idea, rushed to the laboratory, and performed the experiment.

Figure 2.9 Loewi's experiment demonstrating that nerves send messages by releasing chemicals

Loewi stimulated the vagus nerve to one frog's heart, decreasing the heartbeat. When he transferred fluid from that heart to another frog's heart, he observed a decrease in its heartbeat.



Loewi stimulated a frog's vagus nerve, thereby decreasing the heart rate. He collected fluid from around that heart, transferred it to a second frog's heart, and found that the fluid decreased the second frog's heart rate, as depicted in Figure 2.9. Then Loewi stimulated the accelerator nerve to the first frog's heart, increasing the heart rate. When he collected fluid and transferred it to the second frog's heart, its heart rate increased. That is, stimulating one nerve released something that inhibited heart rate, and stimulating a different nerve released something that increased heart rate. Loewi concluded that nerves send messages by releasing chemicals.

Loewi later remarked that if he had thought of this experiment in the light of day, he probably would have dismissed it as unrealistic (Loewi, 1960). Even if synapses did release chemicals, his daytime reasoning went, they probably did not release much. Fortunately, by the time he realized that the experiment should not work, he knew that it did work. It earned him a Nobel Prize.

Despite Loewi's work, most researchers over the next three decades continued to believe that most synapses were electrical and that chemical synapses were the exception. Finally, in the 1950s, researchers established that chemical transmission predominates throughout the nervous system. That discovery revolutionized our understanding and encouraged research that developed drugs for psychiatric uses (Carlsson, 2001). A small number of electrical synapses do exist, however, as discussed later in this module.

Stop & Check

6. What was Loewi's evidence that neurotransmission depends on the release of chemicals?

See page 61 for the answer.

The Chemical Events at a Synapse

Understanding the chemical events at a synapse is fundamental to understanding the nervous system. Here are the major events:

1. The neuron synthesizes chemicals that serve as neurotransmitters, either in the cell body or at the end of the axon.
2. Action potentials travel down the axon. At the presynaptic terminal, the depolarization enables calcium to enter the cell. Calcium releases neurotransmitters from the terminals and into the **synaptic cleft**, the space between the presynaptic and postsynaptic neurons.
3. The released molecules diffuse across the narrow cleft, attach to receptors, and alter the activity of the postsynaptic neuron in any of several ways.
4. The neurotransmitter molecules separate from their receptors.
5. The neurotransmitter molecules may be taken back into the presynaptic neuron for recycling, or they may diffuse away.
6. Some postsynaptic cells send reverse messages to control the further release of neurotransmitter by presynaptic cells.

Figure 2.10 summarizes these steps. Let's now consider each step in more detail. As we do, we also consider drugs that affect certain steps in this process.

Figure 2.10 Transmission at a synapse

The structure shown in green is an astrocyte that shields the synapse from outside chemicals. The astrocyte also exchanges chemicals with the neurons.

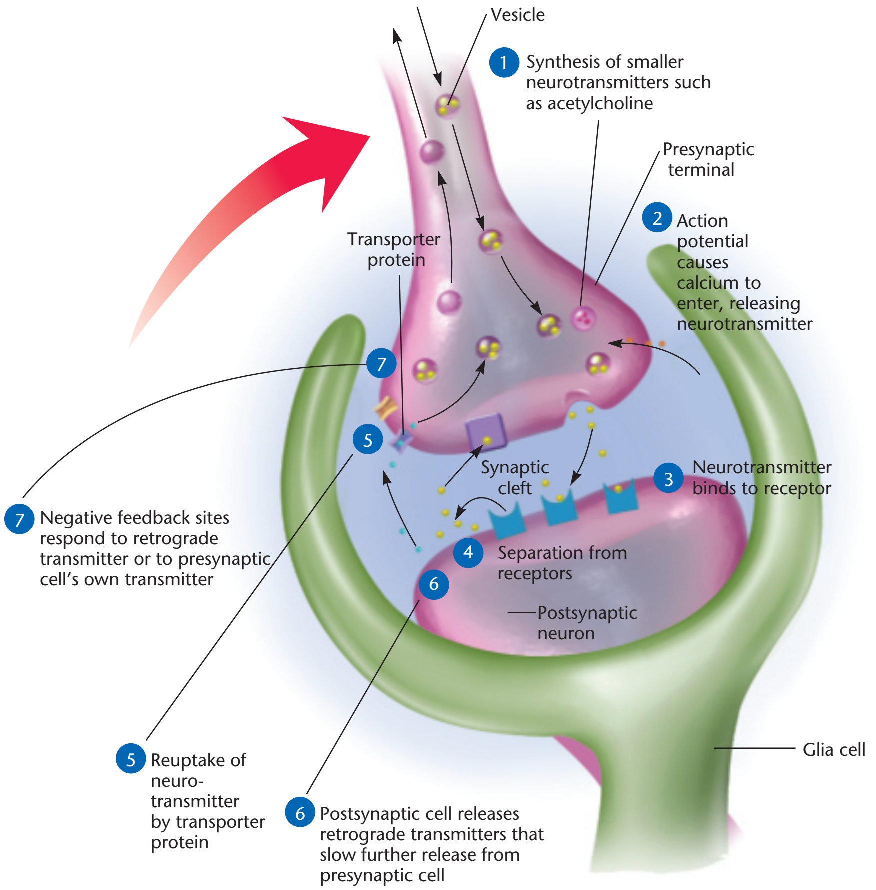

Vesicle
1 Synthesis of smaller neurotransmitters such as acetylcholine
Presynaptic terminal
2 Action potential causes calcium to enter, releasing neurotransmitter
Transporter protein
7
5
Synaptic cleft
3 Neurotransmitter binds to receptor
7 Negative feedback sites respond to retrograde transmitter or to presynaptic cell's own transmitter
4 Separation from receptors
6
Postsynaptic neuron
Glia cell
5 Reuptake of neuro-transmitter by transporter protein
6 Postsynaptic cell releases retrograde transmitters that slow further release from presynaptic cell

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Table 2.1 | Neurotransmitters and neuromodulators

Amino Acids	glutamate, GABA, glycine, aspartate, maybe others
A Modified Amino Acid	acetylcholine
Monoamines (also modified from amino acids)	indoleamines: serotonin catecholamines: dopamine, norepinephrine, epinephrine
Neuropeptides (chains of amino acids)	endorphins, substance P, neuropeptide Y, many others
Purines	ATP, adenosine
Gases	NO (nitric oxide)

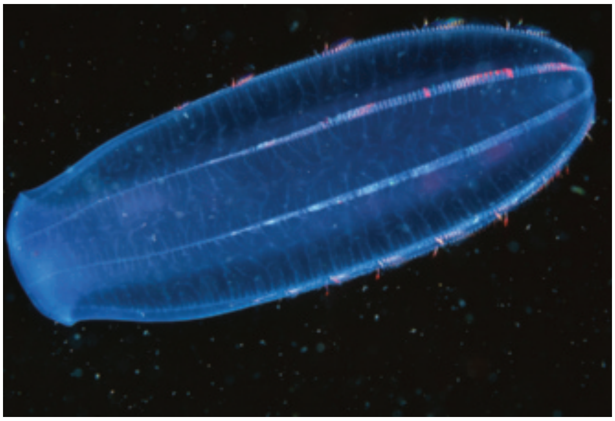
Types of Neurotransmitters

The chemicals that a neuron releases at a synapse are **neurotransmitters** or **neuromodulators**, as listed in Table 2.1 (Borodinsky et al., 2004). Most members of the animal kingdom have all or nearly all the same transmitters that humans have. Ctenophores (Figure 2.11), possibly representative of the earliest, most primitive animals, apparently have only one neurotransmitter, glutamate (Moroz et al., 2014). Glutamate acts even in the plant kingdom, transmitting messages to help the plant react to a damaged part (Toyota et al., 2018).

The oddest transmitter is **nitric oxide** (chemical formula NO), a gas released by many small local neurons. (Do not confuse nitric oxide, NO, with nitrous oxide, N_2O, sometimes known as "laughing gas.") Nitric oxide is toxic in large quantities and difficult to make in a laboratory. Yet, many neurons contain an enzyme that enables them to make it efficiently. Many neurons release nitric oxide when they are stimulated. In addition to influencing other neurons, nitric oxide dilates the nearby blood vessels, thereby increasing blood flow to that brain area (Dawson et al., 1998).

Figure 2.11 A ctenophore

Ctenophores, otherwise known as comb jellies, have a simple nervous system with reportedly only one neurotransmitter, glutamate.



Stop & Check

7. Across species, how much do neurotransmitters vary?

See page 61 for the answer.

Synthesis of Transmitters

Neurons synthesize nearly all neurotransmitters from amino acids, which the body obtains from proteins in the diet. Figure 2.12 illustrates the synthesis of acetylcholine, serotonin, dopamine, epinephrine, and norepinephrine. Note the relationship among epinephrine, norepinephrine, and dopamine—compounds known as **catecholamines**, because they contain a catechol group and an amine group.

Each pathway in Figure 2.12 begins with substances found in the diet. **Acetylcholine**, for example, is synthesized from choline, which is abundant in milk, eggs, and peanuts. The amino acids phenylalanine and tyrosine, present in proteins, are precursors of dopamine, norepinephrine, and epinephrine.

Fewer than one in a thousand neurons release serotonin, but those neurons have axons that branch widely in the nervous system, producing important psychological effects (Okaty et al., 2019). The amino acid *tryptophan*, the precursor to serotonin, crosses the blood–brain barrier by a special transport system that it shares with other large amino acids. Your serotonin levels rise after you eat foods rich in tryptophan, such as soy, and fall after something low in tryptophan, such as maize (American corn). However, tryptophan competes with more abundant amino acids, including phenylalanine, that share the same transport system, so eating more protein is not a reliable way to add tryptophan to the brain. One way to increase tryptophan in the brain is to decrease consumption of phenylalanine. Another is to eat carbohydrates. Carbohydrates increase the release of the hormone *insulin* that takes several competing amino acids out of the bloodstream and into body cells, thus decreasing the competition against tryptophan (Wurtman, 1985).

Several drugs act by altering the synthesis of transmitters. L-dopa, a precursor to dopamine, helps increase the supply of dopamine. It is a helpful treatment for people with Parkinson's disease. AMPT (alpha-methyl-para-tyrosine) temporarily blocks the production of dopamine. It has no therapeutic use, but researchers sometimes use it to study the functions of dopamine.

Stop & Check

8. Name the three catecholamine neurotransmitters.

See page 61 for the answer.

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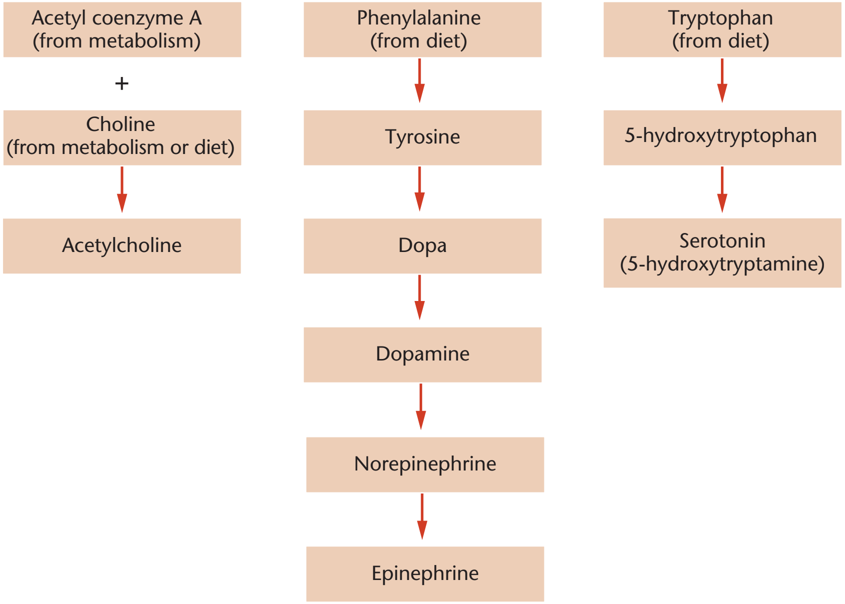
Figure 2.12 Synthesis of acetylcholine, dopamine, norepinephrine, epinephrine, and serotonin

Arrows represent chemical reactions.

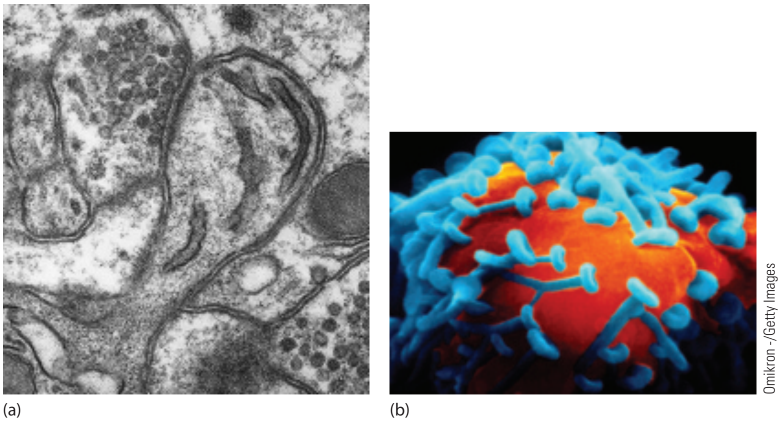

Acetyl coenzyme A
(from metabolism)
+
Choline
(from metabolism or diet)
Acetylcholine
Phenylalanine
(from diet)
Tyrosine
Dopa
Dopamine
Norepinephrine
Epinephrine
Tryptophan
(from diet)
5-hydroxytryptophan
Serotonin
(5-hydroxytryptamine)

Storage of Transmitters

Most neurotransmitters are synthesized in the presynaptic terminal, near the point of release. The presynaptic terminal stores high concentrations of neurotransmitter molecules in **vesicles**, tiny nearly spherical packets (Figure 2.13). Nitric oxide is an exception to this rule. Neurons release nitric oxide as soon as they form it instead of storing it. The presynaptic terminal also holds much neurotransmitter outside the vesicles.

Figure 2.13 Anatomy of a synapse

(a) An electron micrograph showing a synapse from the cerebellum of a mouse. The small round structures are vesicles. (b) Electron micrograph showing axon terminals onto the soma of a neuron.


(a) (b)

Omikron -/Getty Images

(**Source:** Dr. Dennis Landis)

Release of Transmitters

An action potential by itself does not release the neurotransmitter at the end of the axon. Rather, depolarization opens voltage-dependent calcium channels in the presynaptic terminal. The calcium entry causes **exocytosis**—a burst of release of neurotransmitter from the presynaptic neuron.

The released neurotransmitter diffuses across the synaptic cleft to the postsynaptic membrane, where it attaches to a receptor. The neurotransmitter takes no more than 0.01 ms to diffuse across the cleft, which is only 20 to 30 nanometers (nm) wide. Remember, Sherrington did not believe chemical processes could be fast enough to account for the activity at synapses. He did not imagine such a narrow gap through which chemicals could diffuse so quickly.

For many years, investigators believed that each neuron released just one neurotransmitter, but later researchers found that many, probably most, neurons release a combination of two or more transmitters. The result could be immediate brief excitation followed by slower inhibition, or other complex messages. Some neurons simultaneously release an excitatory transmitter and an inhibitory transmitter, the equivalent of saying "yes" and "no" at the same time (Kim et al., 2022).

Stop & Check

9. When the action potential reaches the presynaptic terminal, which ion must enter the presynaptic terminal to evoke release of the neurotransmitter?

See page 61 for the answer.

Effects on the Postsynaptic Cell

Sherrington's concept of the synapse was simple: Input produced excitation or inhibition—in other words, an on/off system. When Eccles recorded from individual cells, he happened to choose cells that produced only brief EPSPs and IPSPs—again, just on/off. The discovery of chemical transmission at synapses didn't change that, at first. Researchers discovered more and more neurotransmitters and wondered, "Why does the nervous system use so many chemicals, if they all produce the same type of message?" Eventually they learned that the messages are not all the same.

The effect of a neurotransmitter depends on how it affects its receptor. When the neurotransmitter attaches to its receptor, the receptor may open a channel—exerting an *ionotropic* effect—or it may produce a slower but longer effect—a *metabotropic* effect.

Ionotropic Effects

At one type of receptor, neurotransmitters exert **ionotropic effects**, corresponding to the brief on/off effects that Sherrington and Eccles studied. Imagine a paper bag that is twisted shut at the top. If you untwist it, the opening grows larger so that something can go into or come out of the bag. An ionotropic receptor is like that. When the neurotransmitter binds to an ionotropic receptor, it twists the receptor just enough to open its central channel, which has a size and shape that lets one type of ion pass through. In contrast to the voltage-gated channels along an axon, the channels controlled by a neurotransmitter are **transmitter-gated** or **ligand-gated**. (A *ligand* is a chemical that binds to something.) When the neurotransmitter attaches, it opens a channel. Ionotropic effects begin quickly, often within less than a millisecond after the transmitter attaches (Lisman et al., 2007). The effects decay quickly, with a half-life of about 5 ms.

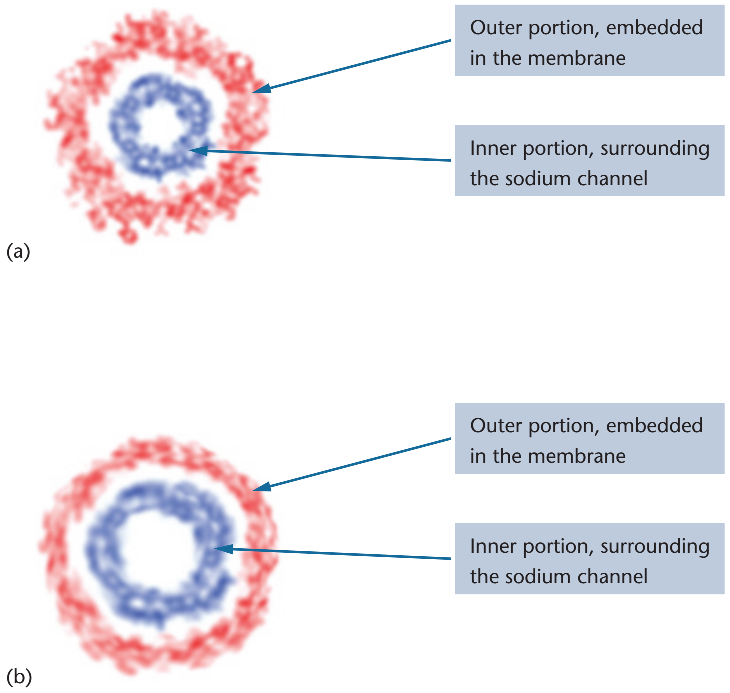
Most of the brain's excitatory ionotropic synapses use the *glutamate*, the most abundant neurotransmitter in the nervous system. Glutamate opens sodium channels. Most of the inhibitory ionotropic synapses use the neurotransmitter GABA (gamma-aminobutyric acid), which opens chloride channels (Wong et al., 2018). Glycine is another inhibitory transmitter, found mostly in the spinal cord (Moss and Smart, 2001). Acetylcholine is excitatory in most cases and inhibitory at others. Figure 2.14a shows an acetylcholine receptor (hugely magnified), as it would appear if you were looking down at it from within the synaptic cleft. Its outer portion (in red) is embedded in the neuron's membrane, and its inner portion (in purple) surrounds the sodium channel. When the receptor is at rest, the inner portion coils together tightly enough to block sodium passage. When acetylcholine attaches as in Figure 2.14b, the receptor folds out, widening the sodium channel (Miyazawa et al., 2003).

Metabotropic Effects and Second Messenger Systems

Other receptors control **metabotropic effects** by initiating a sequence of metabolic reactions that start more slowly

Figure 2.14 The acetylcholine receptor

(a) A cross section of the receptor at rest, as viewed from the synaptic cleft. The membrane surrounds it. (b) A similar view after acetylcholine has attached to the side of the receptor, opening the central channel wide enough for sodium to pass through.


Outer portion, embedded in the membrane
Inner portion, surrounding the sodium channel
(a)
Outer portion, embedded in the membrane
Inner portion, surrounding the sodium channel
(b)

(**Source:** From "Structure and gating mechanism of the acetylcholine receptor pore," by A. Miyazawa, Y. Fujiyoshi, and N. Unwin, 2003, *Nature, 423*, pp. 949–955.)

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but last longer than ionotropic effects. The chemicals that affect these receptors are often called neuromodulators, to distinguish them from the fast effects of the neurotransmitters at ionotropic synapses. Metabotropic effects emerge slowly over 100 ms or more after the release of the transmitter (Liu et al., 2021). Typically, the effects last a few seconds, sometimes longer. Some neuropeptides exert effects that last 20 minutes or more. Whereas most ionotropic effects depend on either glutamate or GABA, metabotropic synapses use many chemicals, including dopamine, norepinephrine, and serotonin, neuropeptides . . . and sometimes glutamate and GABA too.

Apologies if you find this analogy silly, but it might help clarify metabotropic synapses: Imagine a large room. You are outside the room holding a stick that goes through a hole in the wall and attaches to the hinge of a cage. If you shake the stick, you open that cage and release an angry dog. The dog runs around waking up all the rabbits in the room, which then scurry around causing all kinds of further action. A metabotropic receptor acts like that. When a neurotransmitter attaches to a metabotropic receptor, it bends the receptor protein that goes through the membrane of the cell. The other side of that receptor is attached to a **G protein**—a protein coupled to guanosine triphosphate (GTP), an energy-storing molecule. Bending the receptor protein detaches that G protein, which is then free to take its energy elsewhere in the cell, as shown in Figure 2.15. The result of that G protein is increased concentration of a **second messenger**, such as cyclic adenosine monophosphate (cyclic AMP), inside the cell. Just as the "first messenger" (the neurotransmitter) carries information to the postsynaptic cell, the second messenger communicates to areas within the cell. It may open or close ion channels in the membrane, or it may activate or inactivate part of a chromosome. Note the contrast: An ionotropic synapse has effects localized to one point on the membrane, whereas a metabotropic synapse, by way of its second messenger, influences activity in much or all of the cell and over a longer time.

Whereas glutamate and GABA are released at the axon terminal, neuromodulators can be released by dendrites, by the cell body, or by the sides of the axon, and they diffuse to receptors in a wider area, not just a receptor immediately next to the point of release. A single action potential by one axon would release only a tiny amount of transmitter with little effect. However, a cluster of related axons might fire a burst of action potentials, releasing a cloud of the neuromodulator that diffuses to many receptors (Liu et al., 2021). Table 2.2 summarizes neurotransmitters and neuromodulators.

Ionotropic and metabotropic synapses contribute to different aspects of behavior. For vision and hearing, the brain needs immediate, brief information, the kind that ionotropic synapses bring. Metabotropic synapses are suited for more enduring effects such as taste (Huang et al., 2005), smell, and pain (Levine et al., 1993), where the exact timing is less important. Metabotropic effects are also important for arousal, attention, hunger, thirst, and emotion—functions that arise slowly and last longer than a sensation.

Figure 2.15 Sequence of events at a metabotropic synapse, using a second messenger within the postsynaptic neuron

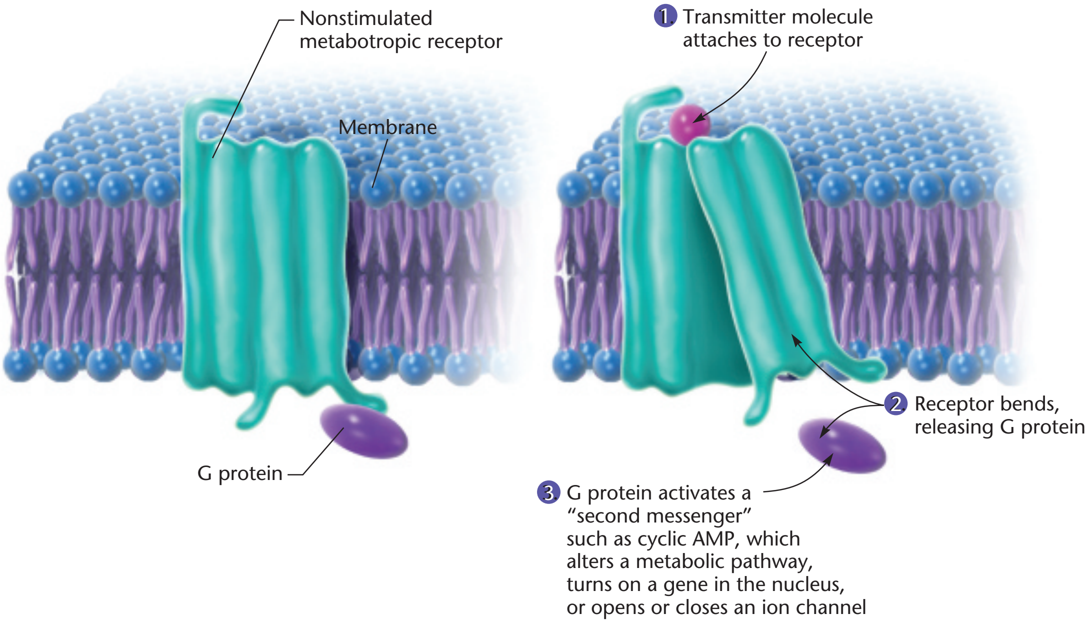
Nonstimulated metabotropic receptor
Membrane
G protein
① Transmitter molecule attaches to receptor
② Receptor bends, releasing G protein
③ G protein activates a "second messenger" such as cyclic AMP, which alters a metabolic pathway, turns on a gene in the nucleus, or opens or closes an ion channel

Table 2.2 | Neurotransmitters and neuromodulators

	Neurotransmitters	Neuromodulators
Released by	Axon terminal	Cell body, dendrites, and sides of axon
Receptors	Immediately adjacent	Spread out
Onset of effects	Sudden	Gradual
Duration of effects	A few milliseconds	Seconds to minutes

Stop & Check

10. How do ionotropic and metabotropic synapses differ in speed and duration of effects?
11. What are second messengers?
12. Ionotropic synapses are most important for what types of behavior?

See page 61 for the answer.

Variation in Receptors

Many neurotransmitters attach to more than one type of receptor. The brain has seven types of serotonin receptors, each with subtypes, mostly metabotropic types but one ionotropic type (Sharp and Barnes, 2020). Because different receptors control different functions, drugs can have specialized effects on behavior. The drug *ondansetron* that blocks just serotonin receptor type 3 prevents nausea, without much other effect. Antidepressant drugs exert their benefits by stimulating serotonin receptor type 2A.

A given receptor can have different effects for different people, or even in different parts of one person's brain, because of differences in the hundreds of proteins that surround synapses, tether the presynaptic neuron to the postsynaptic neuron, and guide neurotransmitter molecules to their receptors (O'Rourke et al., 2012; Wilhelm et al., 2014). Genetic variations in synaptic proteins have been linked to variations in anxiety, sleep, and other aspects of behavior.

Drugs that Bind to Receptors

A drug that chemically resembles a neurotransmitter can bind to its receptor. Many **hallucinogenic drugs**—that is, drugs that distort perception, such as lysergic acid diethylamide (LSD)—chemically resemble serotonin. They attach to serotonin type 2A (5-HT$_{2A}$) receptors and stimulate them for longer-than-normal durations. LSD enhances connections among brain areas that ordinarily do not communicate much with one another. A possible explanation for the hallucinogenic effect is that the increased spontaneous communication dominates over the input coming from the sense organs (Carhart-Harris et al., 2016; Tagliazucchi et al., 2016).

Opiate drugs are derived from or related to chemicals in the opium poppy. Familiar opiates include morphine, heroin, and methadone. People used morphine and other opiates for centuries without knowing how the drugs affected the brain. Then researchers found that opiates attach to specific receptors in the brain (Pert and Snyder, 1973). It was a safe guess that vertebrates had not evolved such receptors just to enable us to become drug addicts. Soon investigators found that the brain produces its own neuropeptides, now known as *endorphins* (a contraction of *endo*genous m*orphines*), that bind to the same receptors as opiates. This discovery was important because it indicated that opiates relieve pain by acting on receptors in the brain as well as in the skin. This finding also paved the way for the discovery of other neuropeptides that regulate emotions and motivations.

Stop & Check

13. How do LSD and opiate drugs influence behavior?

See page 61 for the answer.

Inactivation and Reuptake of Neurotransmitters

A neurotransmitter does not linger after activating its receptor. After the release of glutamate or GABA, specialized **transporter** proteins quickly move the molecules back into the presynaptic cell. This process, called **reuptake**, serves two purposes. One is recycling, so that the presynaptic neuron has transmitters available for release again. The other is to halt the effect on the postsynaptic cell. At ionotropic synapses, timing is critical for both the onset and the offset.

Acetylcholine undergoes reuptake only after the enzyme *acetylcholinesterase* (a-SEE-til-ko-lih-NES-teh-raze) breaks it into two fragments: acetate and choline. The choline diffuses back to the presynaptic neuron, which reattaches it to form acetylcholine again. Although reuptake is efficient, it takes time, and the presynaptic neuron does not reabsorb every molecule it releases. A sufficiently rapid series of action potentials at a synapse can deplete the neurotransmitter faster than the presynaptic cell replenishes it, impairing transmission (Liu and Tsien, 1995).

After serotonin or the catecholamines (dopamine, norepinephrine, and epinephrine) activate a receptor, the next step varies. The presynaptic neuron takes up much or most

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of the released neurotransmitter molecules for reuse. The reuptake process varies among individuals and from one brain area to another, but it is slower than reuptake of glutamate or GABA (Liu et al., 2021). In many cases the slow reuptake is a benefit, because it enables the chemicals to build up enough concentration to have significant effects on their receptors. Enzymes break down any transmitter molecules that the transporters do not reuptake, and the breakdown products wash away and eventually show up in the blood and urine. Neuropeptides simply diffuse away from the membrane, without reuptake. Because resynthesizing these large molecules takes time, a neuron can temporarily exhaust its supply.

Stimulant drugs, including **amphetamine** and **cocaine**, inhibit the transporters for dopamine, serotonin, and norepinephrine, decreasing reuptake and prolonging the effects of the neurotransmitters (Beuming et al., 2008; Schmitt and Reith, 2010; Zhao et al., 2010). Prolonging the dopamine effects produces increased arousal. Most antidepressant drugs also block reuptake of one or more neurotransmitters, but more weakly than amphetamine and cocaine do.

When stimulant drugs prevent the usual amount of dopamine reuptake, enzymes break down much of the extra dopamine that stays in the synaptic cleft. The presynaptic cell needs extra time to replenish its supply. A few hours after taking a stimulant drug, a user has less than usual dopamine and enters a withdrawal state, marked by reduced energy, reduced motivation, and mild depression.

Methylphenidate (Ritalin), another stimulant drug, is often prescribed for people with attention deficit/hyperactivity disorder. Methylphenidate blocks the reuptake of dopamine in the same way that cocaine does, at the same brain receptors. The differences between methylphenidate and cocaine relate to the time course. Cocaine users typically sniff it or inject it to produce a rapid rush of effect on the brain. People taking methylphenidate pills experience more gradual effects without a sudden rush. Still, blocking reuptake has a consequence. A methadone pill increases arousal at first, but a few hours later the user may experience reduced energy and motivation.

Stop & Check

14. What happens to acetylcholine molecules after they stimulate a postsynaptic receptor?
15. What happens to serotonin and catecholamine molecules after they stimulate a postsynaptic receptor?
16. How do amphetamine and cocaine influence synapses?
17. Why is methylphenidate generally less disruptive to behavior than cocaine, despite the drugs' similar mechanisms?

See page 61 for the answer.

Negative Feedback from the Postsynaptic Cell

Suppose someone sends you an email message and then, worried that you might not have received it, sends it again and again. To prevent cluttering your inbox, you might add a system that provides an automatic answer, "Yes, I got your message. Don't send it again."

A couple of mechanisms in the nervous system serve that function. First, many presynaptic terminals have receptors sensitive to the same transmitter they release. These receptors are known as **autoreceptors**—receptors that respond to the released transmitter by inhibiting further synthesis and release. That is, they provide negative feedback (Kubista and Boehm, 2006).

Second, some postsynaptic neurons respond to stimulation by releasing chemicals that travel back to the presynaptic terminal to inhibit further release of transmitter. Two reverse transmitters are anandamide (from the Sanskrit word *anana*, meaning "bliss") and 2-AG (*sn*-2 arachidonylglycerol). **Cannabinoids**, the active chemicals in marijuana, mimic the effects of these reverse transmitters, telling a presynaptic neuron, "I received your message. Stop sending it." The presynaptic cell, unaware that it hadn't sent a message, cancels whatever it had been about to send. In this way, the chemicals in marijuana decrease the release of both glutamate and GABA (Lutz et al., 2015). The behavioral results vary, but they usually include decreased anxiety.

Stop & Check

18. How do cannabinoids affect neurons?

See page 61 for the answer.

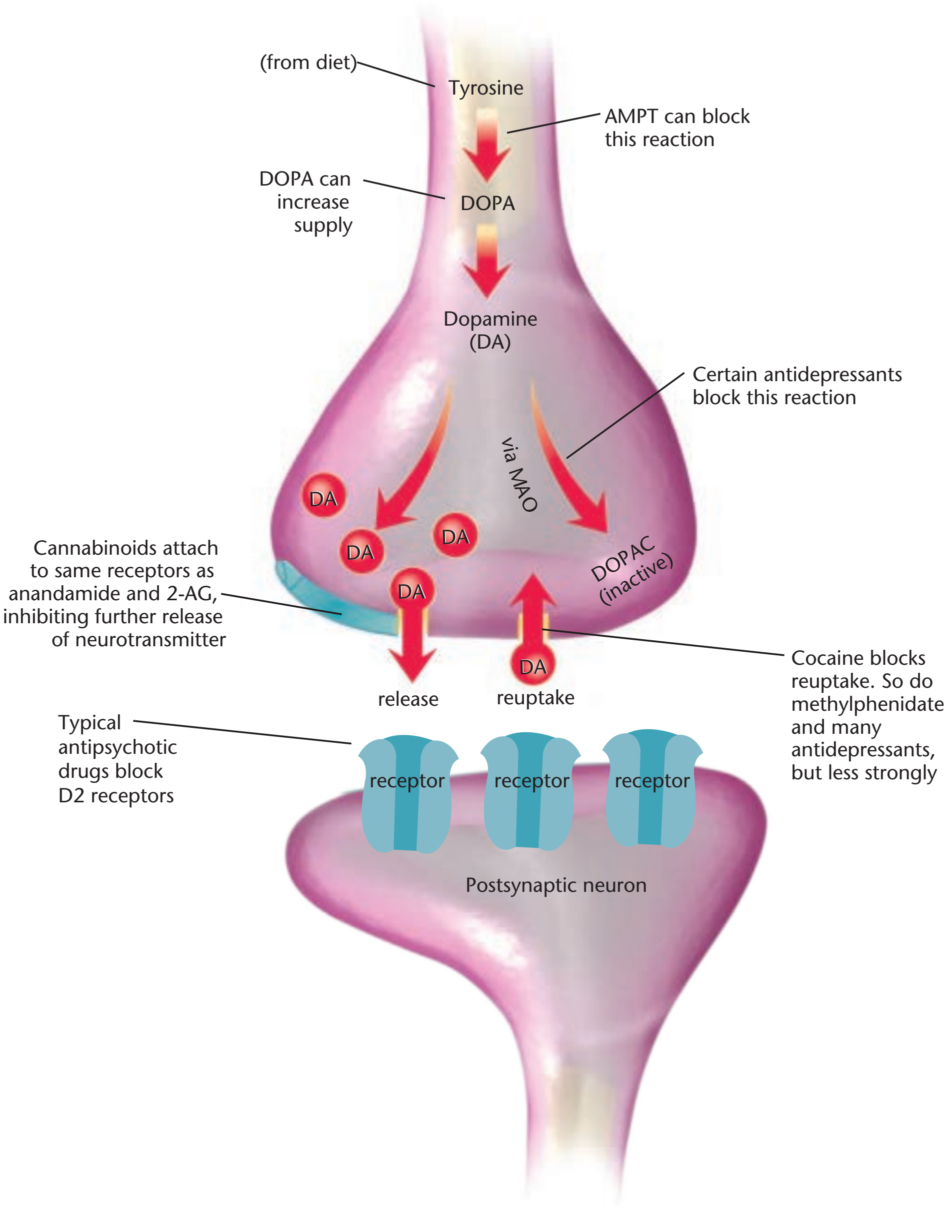
Figure 2.16 summarizes some of the ways in which drugs affect dopamine transmission, including effects on synthesis, release, action on postsynaptic receptors, reuptake, and breakdown. Table 2.3 also summarizes effects of some common drugs.

Electrical Synapses

At the start of this module, you learned that Sherrington was wrong to assume that synapses convey messages electrically. He wasn't completely wrong. A few special-purpose synapses do operate electrically. Because electrical transmission is faster than even the fastest chemical transmission, electrical synapses have evolved in cases where exact synchrony between cells is important. For example, some of the cells that control your breathing are synchronized by electrical synapses. (It's important

Figure 2.16 Effects of some drugs on dopamine transmission

Unlike glutamate and GABA receptors, dopamine receptors are not all immediately adjacent to the point of release.


(from diet)
Tyrosine
AMPT can block this reaction
DOPA can increase supply
DOPA
Dopamine (DA)
Certain antidepressants block this reaction
via MAO
DOPAC (inactive)
DA
DA
DA
DA
DA
Cannabinoids attach to same receptors as anandamide and 2-AG, inhibiting further release of neurotransmitter
release
reuptake
Cocaine blocks reuptake. So do methylphenidate and many antidepressants, but less strongly
Typical antipsychotic drugs block D2 receptors
receptor
receptor
receptor
Postsynaptic neuron

to inhale on the left side at the same time as on the right side.) Many animal species have electrical synapses in the system responsible for coordinating rapid escape movements (Pereda, 2014).

At an electrical synapse, the membrane of one neuron makes direct contact with the membrane of another, as shown in Figure 2.17. This contact is called a **gap junction**. Large pores of the membrane of one neuron line up precisely with pores in the membrane of the other cell. These pores are large enough for sodium and other ions to pass readily, and the pores are always open. Whenever one of the neurons is depolarized, sodium ions from that cell pass immediately into the other neuron and depolarize it, too. As a result, the two neurons act as if they were a single neuron.

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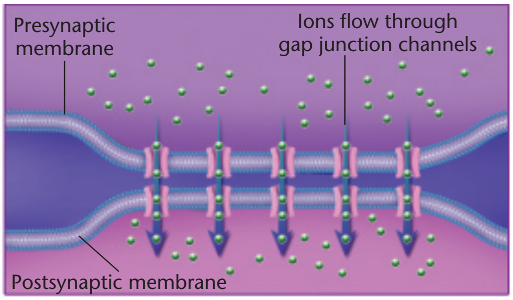
Table 2.3 | Summary of Some Drugs and Their Effects

Drugs	Main Synaptic Effects
Amphetamine	Blocks reuptake of dopamine and several other transmitters
Cocaine	Blocks reuptake of dopamine and several other transmitters
Methylphenidate (Ritalin)	Blocks reuptake of dopamine and others, but gradually
MDMA (“Ecstasy”)	Releases dopamine, serotonin, and norepinephrine
Nicotine	Stimulates nicotinic-type acetylcholine receptor, which increases dopamine release
Opiates (e.g., heroin, morphine)	Stimulates endorphin receptors
Cannabinoids (marijuana)	Excites negative-feedback receptors on presynaptic cells
Hallucinogens (e.g., LSD)	Stimulates serotonin type 2A receptors (5-HT_{2A})

Figure 2.17 A gap junction for an electrical synapse


Presynaptic membrane
Ions flow through gap junction channels
Postsynaptic membrane

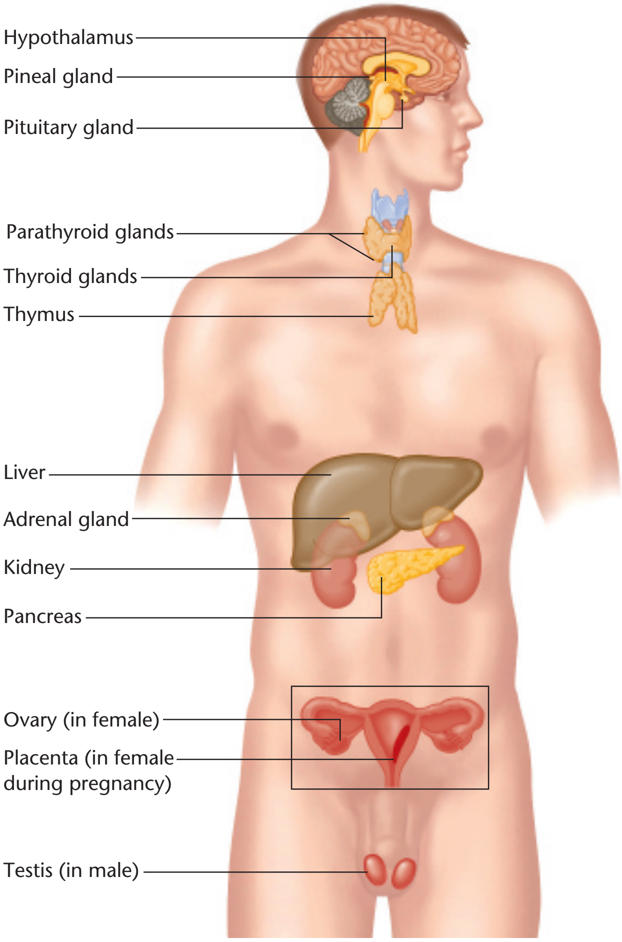
Hormones

Hormonal influences resemble synaptic transmission in many ways, and many chemicals serve as both hormones and neurotransmitters. A **hormone** is a chemical secreted by cells in one part of the body and conveyed by the blood to influence other cells. A neurotransmitter is like a telephone signal: It conveys a message from the sender to the intended receiver. Hormones function more like radio waves: They convey a message to any receiver tuned to the right station.

Figure 2.18 shows the major **endocrine** (hormone-producing) **glands**. Table 2.4 lists hormones that become relevant in other chapters of this book. (A complete list would be lengthy and uncertain. The body releases tiny amounts of some chemicals that might or might not act as hormones.)

Just as circulating hormones modify brain activity, hormones secreted by the brain control the secretion of other hormones. The **pituitary gland**, attached

Figure 2.18 Location of some major endocrine glands

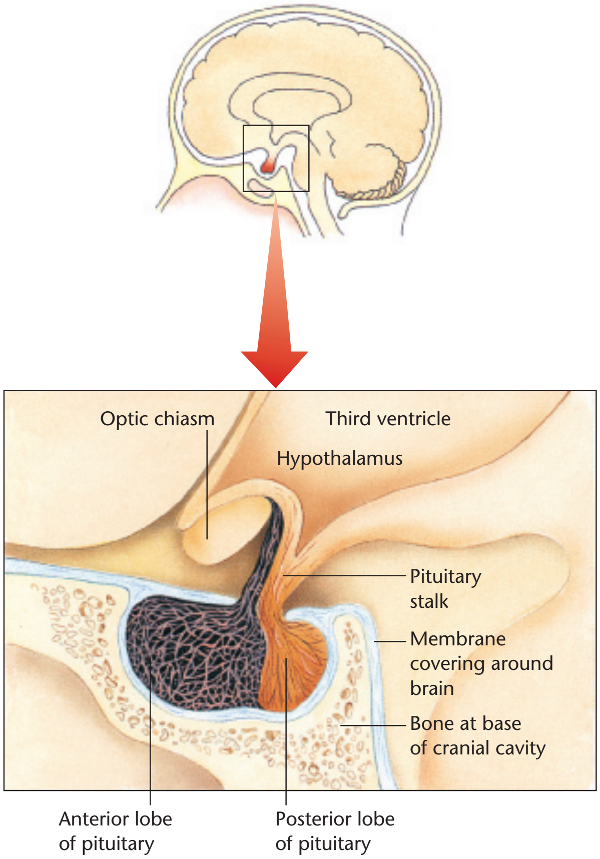

Hypothalamus
Pineal gland
Pituitary gland
Parathyroid glands
Thyroid glands
Thymus
Liver
Adrenal gland
Kidney
Pancreas
Ovary (in female)
Placenta (in female during pregnancy)
Testis (in male)

(**Source:** Starr and Taggart, 1989)

Table 2.4 | Selective List of Hormones

Organ	Hormone	Hormone Functions (partial)
Hypothalamus	Various releasing hormones	Promote/inhibit release of hormones from pituitary
Anterior pituitary	Thyroid-stimulating hormone	Stimulates thyroid gland
	Luteinizing hormone	Stimulates ovulation
	Follicle-stimulating hormone	Promotes ovum maturation (female), sperm production (male)
	ACTH	Increases steroid hormone production by adrenal gland
	Prolactin	Increases milk production
	Growth hormone	Increases body growth
Posterior pituitary	Oxytocin	Uterine contractions, milk release, sexual pleasure
	Vasopressin	Raises blood pressure, decreases urine volume
Pineal	Melatonin	Sleepiness; also role in puberty
Adrenal cortex	Aldosterone	Reduces release of salt in the urine
	Cortisol	Elevated blood sugar and metabolism
Adrenal medulla	Epinephrine, norepinephrine	Similar to actions of sympathetic nervous system
Pancreas	Insulin	Helps glucose enter cells
	Glucagon	Helps convert stored glycogen into blood glucose
Ovary	Estrogens and progesterone	Female sexual characteristics and pregnancy
Testis	Testosterone	Male sexual characteristics and pubic hair
Kidney	Renin	Regulates blood pressure, contributes to hypovolemic thirst
Fat cells	Leptin	Decreases appetite, increases activity

Figure 2.19 The hypothalamus and pituitary gland in the human brain


Optic chiasm
Third ventricle
Hypothalamus
Pituitary stalk
Membrane covering around brain
Bone at base of cranial cavity
Anterior lobe of pituitary
Posterior lobe of pituitary

(**Source:** Starr and Taggart, 1989)

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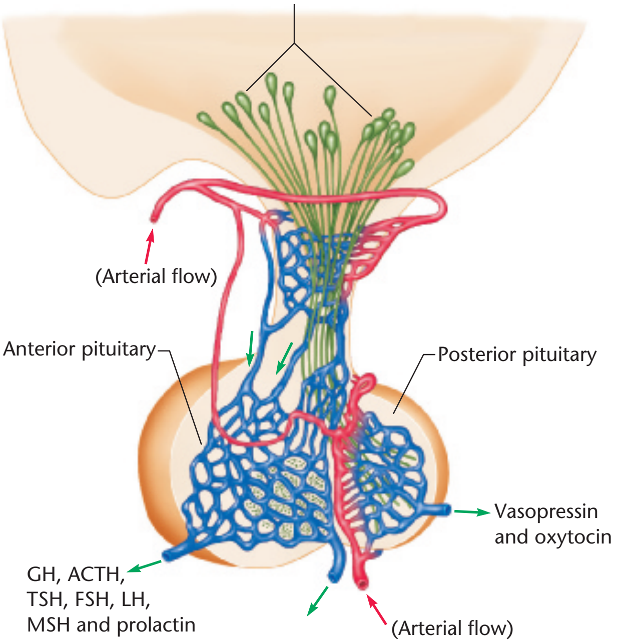
to the hypothalamus (Figure 2.19), has two parts, the **anterior pituitary** and the **posterior pituitary**. The posterior pituitary can be considered an extension of the hypothalamus. Neurons in the hypothalamus synthesize the hormones **oxytocin** and **vasopressin** (also known as antidiuretic hormone), which migrate down axons to the posterior pituitary, which releases them, as illustrated in Figure 2.20. The hypothalamus also synthesizes **releasing hormones** and inhibiting hormones that control the anterior pituitary's release of hormones that control other organs' hormone release (Figure 2.20).

The hypothalamus maintains fairly constant circulating levels of certain hormones through a negative feedback system. For example, when the level of thyroid hormone is low, the hypothalamus releases *TSH-releasing hormone*, which stimulates the anterior pituitary to release TSH, which in turn causes the thyroid gland to secrete more thyroid hormones (Figure 2.21).

Figure 2.20 Pituitary hormones

The hypothalamus produces vasopressin and oxytocin, which travel to the posterior pituitary (really an extension of the hypothalamus). The posterior pituitary releases those hormones in response to neural signals. The hypothalamus also produces releasing hormones and inhibiting hormones that travel to the anterior pituitary, where they control the release of growth hormone, adrenocorticotropin, thyrotropin, follicle-stimulating hormone, luteinizing hormone, melanocyte-stimulating hormone, and prolactin.



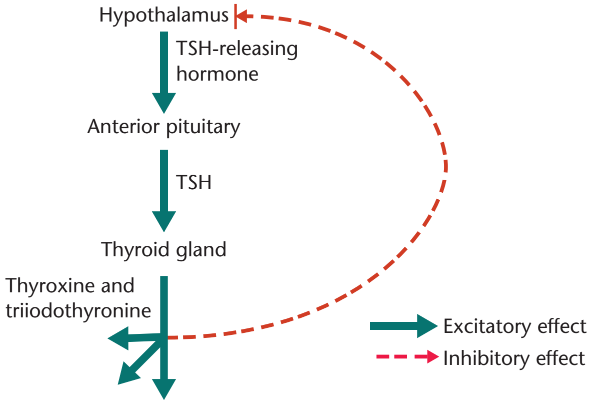
Stop & Check

19. Which part of the pituitary—anterior or posterior—is neural tissue, similar to the hypothalamus? Which part is glandular tissue and produces hormones that control the secretions by other endocrine organs?
20. What do releasing hormones do?

See page 61 for the answer.

Figure 2.21 Negative feedback in the control of thyroid hormones

The hypothalamus secretes a releasing hormone that stimulates the anterior pituitary to release TSH, which stimulates the thyroid gland to release its hormones. Those hormones, in turn, act on the hypothalamus to decrease its secretion of the releasing hormone.



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Module 2.2 | In Closing

Neurotransmitters and Behavior

In the time since Sherrington, we have come a long way in our understanding of synapses. We no longer think of synapses as simple on/off messages. Synaptic messages vary in intensity, speed of onset, and duration. Drugs can modify them in many ways, for good or bad, and so can experiences. Understanding how the nervous system produces our behavior and experiences is largely a matter of understanding synapses.

Summary

1. The great majority of synapses operate by transmitting a chemical neurotransmitter from the presynaptic cell to the postsynaptic cell. Otto Loewi demonstrated chemical transmission by stimulating a frog's heart electrically and then transferring fluids from that heart to another frog's heart. **48**
2. Many chemicals are used as neurotransmitters. Most are amino acids or chemicals derived from amino acids. **50**
3. An action potential opens calcium channels in the axon terminal, and the calcium enables release of neurotransmitters. **51**
4. At ionotropic synapses, a neurotransmitter attaches to a receptor that opens the gates to allow a particular ion, such as sodium, to cross the membrane. Ionotropic effects are fast and brief. Most excitatory ionotropic synapses use glutamate, and most inhibitory ionotropic synapses use GABA. **52**
5. Neuromodulators activate metabotropic receptors, in which a second messenger inside the postsynaptic cell produces slower but longer-lasting changes, compared to ionotropic effects. **52**
6. Several drugs including LSD, antipsychotic drugs, nicotine, and opiate drugs exert their behavioral effects by binding to receptors on the postsynaptic neuron. **54**
7. After a neurotransmitter or neuromodulator activates its receptor, many of the transmitter molecules reenter the presynaptic cell through transporter molecules in the membrane. This process, known as reuptake, enables the presynaptic cell to recycle its neurotransmitter. The process is fast for glutamate and GABA, slower for serotonin and dopamine. Stimulant drugs and many antidepressant drugs inhibit reuptake of certain transmitters. **54**
8. Postsynaptic neurons send chemicals to receptors on the presynaptic neuron to inhibit further release of neurotransmitter. Cannabinoids, found in marijuana, mimic these chemicals. **55**
9. Hormones travel through the blood, affecting receptors in many organs. Their mechanism of effect resembles that of a metabotropic synapse. **57**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

acetylcholine **50**
amino acids **50**
amphetamine **55**
anterior pituitary **59**
autoreceptors **55**
cannabinoids **55**
catecholamines **50**
cocaine **55**
endocrine glands **57**
exocytosis **51**
G protein **53**
gap junction **56**
gases **50**
hallucinogenic drugs **54**
hormone **57**
ionotropic effects **52**
ligand-gated channels **52**
metabotropic effects **52**
methylphenidate **55**
monoamines **50**
neuromodulators **50**
neuropeptides **50**
neurotransmitters **50**
nitric oxide **50**
opiate drugs **54**
oxytocin **59**
pituitary gland **57**
posterior pituitary **59**
purines **50**
releasing hormones **59**
reuptake **54**
second messenger **53**
synaptic cleft **49**
transmitter-gated channels **52**
transporters **54**
vasopressin **59**
vesicles **51**

Thought Questions

1. Suppose axon A enters a ganglion (a cluster of neurons) and axon B leaves on the other side. Shortly after an experimenter stimulates A, an impulse travels down B. We want to know whether B is just an extension of axon A or whether A formed an excitatory synapse on some neuron in the ganglion, whose axon is axon B. How could an experimenter determine the answer? Try to think of more than one good method. Presume that the anatomy within the ganglion is so complex that you cannot simply observe the course of an axon through it.
2. If serotonin axons were destroyed, LSD would still have its full effects. However, if dopamine axons were destroyed, amphetamine and cocaine would lose their effects. Explain the difference.

Stop & Check Answers

6. When Loewi stimulated a nerve that increased or decreased a frog's heart rate, he could withdraw fluid from the area around the heart, transfer it to another frog's heart, and thereby increase or decrease its rate also.
7. Most animals have all or nearly all the same neurotransmitters.
8. Epinephrine, norepinephrine, and dopamine. Do not confuse the term *catecholamine* with *acetylcholine*.
9. Calcium
10. Ionotropic synapses act more quickly and more briefly.
11. Second messengers are chemicals that alter metabolism or gene expression within a postsynaptic neuron. At metabotropic synapses, the neurotransmitter attaches to a receptor and releases a second messenger.
12. Ionotropic synapses are most important when precise timing is important, such as visual or auditory perception.
13. LSD binds to one type of serotonin receptor. Opiates bind to endorphin receptors.
14. The enzyme acetylcholinesterase breaks acetylcholine molecules into two smaller molecules, acetate and choline. The presynaptic neuron then reabsorbs the choline.
15. Most serotonin and catecholamine molecules are reabsorbed by the presynaptic terminal. Some of their molecules are broken down into inactive chemicals, which then diffuse away.
16. They block reuptake of released dopamine, serotonin, and norepinephrine.
17. The effects of a methylphenidate pill rise and fall more slowly than those of cocaine.
18. Cannabinoids released by the postsynaptic neuron attach to receptors on presynaptic neurons, where they inhibit further release of both glutamate and GABA.
19. The posterior pituitary is neural tissue, like the hypothalamus. The anterior pituitary is glandular tissue and produces hormones that control several other endocrine organs.
20. The hypothalamus secretes releasing hormones, which control release of hormones by the pituitary gland.

Module 2.2 | End-of-Module Quiz

1. How did Loewi demonstrate chemical transmission at a synapse?
   a. He transferred fluid from one frog's heart to another's.
   b. He applied adrenalin to muscles and observed the responses.
   c. He chemically analyzed the output from presynaptic neurons.
   d. He made inferences from dogs' reflexive behavior.

2. What are the brain's most abundant excitatory and inhibitory neurotransmitters, respectively?
   a. Glutamate and GABA
   b. Dopamine and serotonin
   c. Acetylcholine and nitric oxide
   d. Glucose and thiamine

3. Which of these is a catecholamine?
   a. GABA
   b. Glutamate
   c. Acetylcholine
   d. Dopamine

4. Why does removing phenylalanine from circulation increase the serotonin in the brain?
   a. When phenylalanine enters fat cells, it triggers the release of hormones.
   b. Phenylalanine and tryptophan compete for entry to the brain.
   c. Enzymes in the liver convert phenylalanine into serotonin.
   d. Phenylalanine stimulates the vagus nerve, which stimulates certain brain areas.

5. Suppose you want to cause the presynaptic terminal of an axon to release its transmitter. How could you do so *without* an action potential?
   a. Decrease the temperature at the synapse.
   b. Use an electrode to produce IPSPs in the postsynaptic neuron.
   c. Inject water into the presynaptic terminal.
   d. Inject calcium into the presynaptic terminal.

6. Which type of synapse is better suited for vision and hearing, and why?
   - **a.** Metabotropic synapses, because they produce quick, brief effects
   - **b.** Metabotropic synapses, because they produce longer lasting effects
   - **c.** Ionotropic synapses, because they produce quick, brief effects
   - **d.** Ionotropic synapses, because they produce longer lasting effects

7. What is a second messenger?
   - **a.** A chemical released by the presynaptic neuron a few milliseconds after release of the first neurotransmitter
   - **b.** A chemical released inside a cell after it is stimulated at a metabotropic synapse
   - **c.** A chemical that travels from the postsynaptic neuron back to the presynaptic neuron
   - **d.** A neuropeptide that affects all neurons in an area

8. How do the effects of neuropeptides differ from those of other transmitters?
   - **a.** Their effects last longer.
   - **b.** They produce first an excitatory effect, and then a prolonged inhibitory effect.
   - **c.** They act mainly by increasing the activity of mitochondria.
   - **d.** They act faster but more briefly.

9. What fact makes it possible to develop drugs with a limited effect, such as suppressing nausea?
   - **a.** The postsynaptic neuron sends a message back to the presynaptic neuron.
   - **b.** Each transmitter attaches to more than one type of receptor.
   - **c.** Metabotropic synapses act by means of a second messenger.
   - **d.** A neuron releases neuropeptides from the dendrites as well as the axon.

10. A transporter protein produces which of the following?
    - **a.** Reuptake
    - **b.** The refractory period
    - **c.** Negative feedback
    - **d.** Spatial summation

11. Except for the magnitude and speed of effects, methylphenidate (Ritalin) affects synapses the same way as which drug?
    - **a.** Heroin
    - **b.** Cocaine
    - **c.** Nicotine
    - **d.** Marijuana

12. How do cannabinoids affect synapses?
    - **a.** They stimulate serotonin synapses at inappropriate times or for long durations.
    - **b.** They increase spatial summation for excitation in separate dendrites.
    - **c.** They cause the release of second messengers in the postsynaptic neuron.
    - **d.** They inhibit the release of both excitatory and inhibitory transmitters.

13. Electrical synapses are important when the nervous system needs to accomplish which of the following?
    - **a.** Inhibition of competing behaviors
    - **b.** Synchrony between neurons
    - **c.** Complex reasoning
    - **d.** Long-lasting activation

14. Which of these is composed of neural tissue, as opposed to glandular tissue?
    - **a.** The anterior pituitary
    - **b.** The posterior pituitary
    - **c.** The pancreas
    - **d.** The adrenal gland

15. What part of the brain produces releasing hormones that control the pituitary gland?
    - **a.** Cerebral cortex
    - **b.** Hippocampus
    - **c.** Hypothalamus
    - **d.** Amygdala

Answers: 1a, 2a, 3d, 4b, 5d, 6c, 7b, 8a, 9b, 10a, 11b, 12d, 13b, 14b 15c.

Suggestion for Further Reading

Berkowitz, A. (2016). *Governing behavior: How nerve cell dictatorships and democracies control everything we do.* Cambridge, MA: Harvard University Press. Discusses many examples illustrating how synaptic connections decide between one course of action and another.

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Chapter 3

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2 IMA 17

New methods allow researchers to examine living brains.
(TEK IMAGE/Science Source)

Anatomy and Research Methods

Chapter Outline

Module 3.1

Structure of the Vertebrate Nervous System

Terminology to Describe the Nervous System
The Spinal Cord
The Autonomic Nervous System
The Hindbrain
The Midbrain
The Forebrain
The Ventricles
In Closing: Learning Neuroanatomy

Module 3.2

The Cerebral Cortex

Organization of the Cerebral Cortex
The Occipital Lobe
The Parietal Lobe
The Temporal Lobe
The Frontal Lobe
How Do the Parts Work Together?
In Closing: Functions of the Cerebral Cortex

Module 3.3

Research Methods

Effects of Brain Damage
Effects of Brain Stimulation
Recording Brain Activity
Correlating Brain Anatomy with Behavior
In Closing: Research Methods and Progress

Learning Objectives

After studying this chapter, you should be able to:

1. Define the terms used to describe brain anatomy.
2. Describe the structure of the spinal cord.
3. Describe the structure and functions of the autonomic nervous system.
4. List the major components of the hindbrain, midbrain, and forebrain.
5. Distinguish between the laminae and columns of the cortex.
6. List the four lobes of the cerebral cortex and describe their principal functions.
7. Describe the binding problem and explain its theoretical importance.
8. Describe major methods for studying the relationship between brain activity and behavior.
9. Note the strengths and limitations of each method.

Learning **neuroanatomy** (the anatomy of the nervous system) from a book is like learning geography from a road map. A map can tell you that Mystic, Georgia, is about 40 km north of Enigma, Georgia, and a book can tell you that the habenula is about 4.6 mm from the interpeduncular nucleus in a rat's brain (proportionately farther in a human brain). But these little gems of information will seem mysterious and enigmatic unless you are interested in that part of Georgia or that area of the brain.

This chapter is more like a world globe than a road map, describing the larger structures and some distinctive features of each. Still, it will introduce a great many terms and facts. You cannot expect to learn them all at once, and you should review this chapter repeatedly.

The first module introduces key neuroanatomical terms and outlines overall structures of the nervous system. In the second module, we concentrate on the cerebral cortex, the largest part of the mammalian central nervous system. The third module outlines research methods that explore the functions of brain areas.

Module 3.1

Structure of the Vertebrate Nervous System

Learning Objectives

After studying this module, you should be able to:

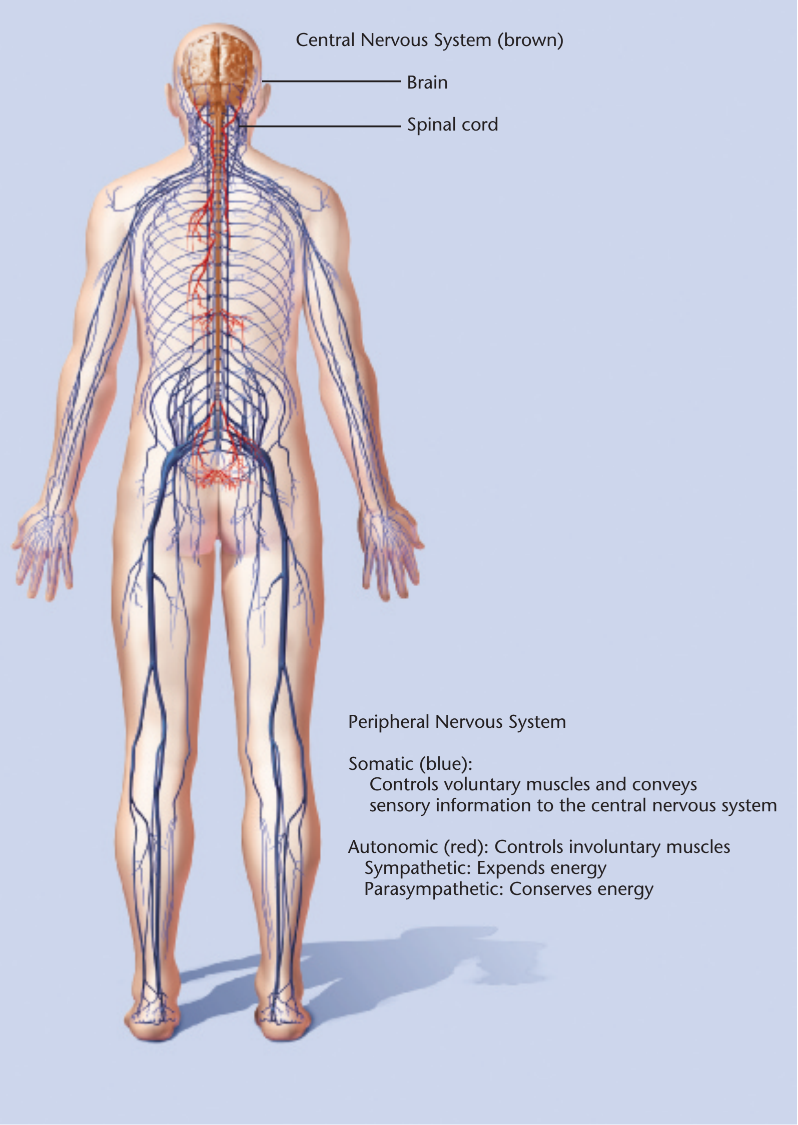
1. Define the terms used to describe brain anatomy.
2. Describe the structure of the spinal cord.
3. Describe the structure and functions of the autonomic nervous system.
4. List the major components of the hindbrain, midbrain, and forebrain.

Your nervous system includes a huge number of neurons and an even huger number of synapses. How do they all work together to make one behaving unit? Does each neuron have a unique function? Does each brain area have a unique function? Or does the brain operate as an undifferentiated whole?

The answer is something between those extremes. Consider an analogy to human society: Each person has a specialty, such as teacher, farmer, or nurse, but no one performs any function without the cooperation of many others. Similarly, brain areas and neurons have specialized functions, but they perform those roles by connections with other areas.

Figure 3.1 The human nervous system

The central nervous system consists of the brain and spinal cord. The peripheral nervous system is the nerves outside the brain and spinal cord.


Central Nervous System (brown)
Brain
Spinal cord
Peripheral Nervous System
Somatic (blue):
Controls voluntary muscles and conveys sensory information to the central nervous system
Autonomic (red): Controls involuntary muscles
Sympathetic: Expends energy
Parasympathetic: Conserves energy

Terminology to Describe the Nervous System

For vertebrates, we distinguish the central nervous system from the peripheral nervous system (Figure 3.1). The **central nervous system (CNS)** is the brain and the spinal cord. The

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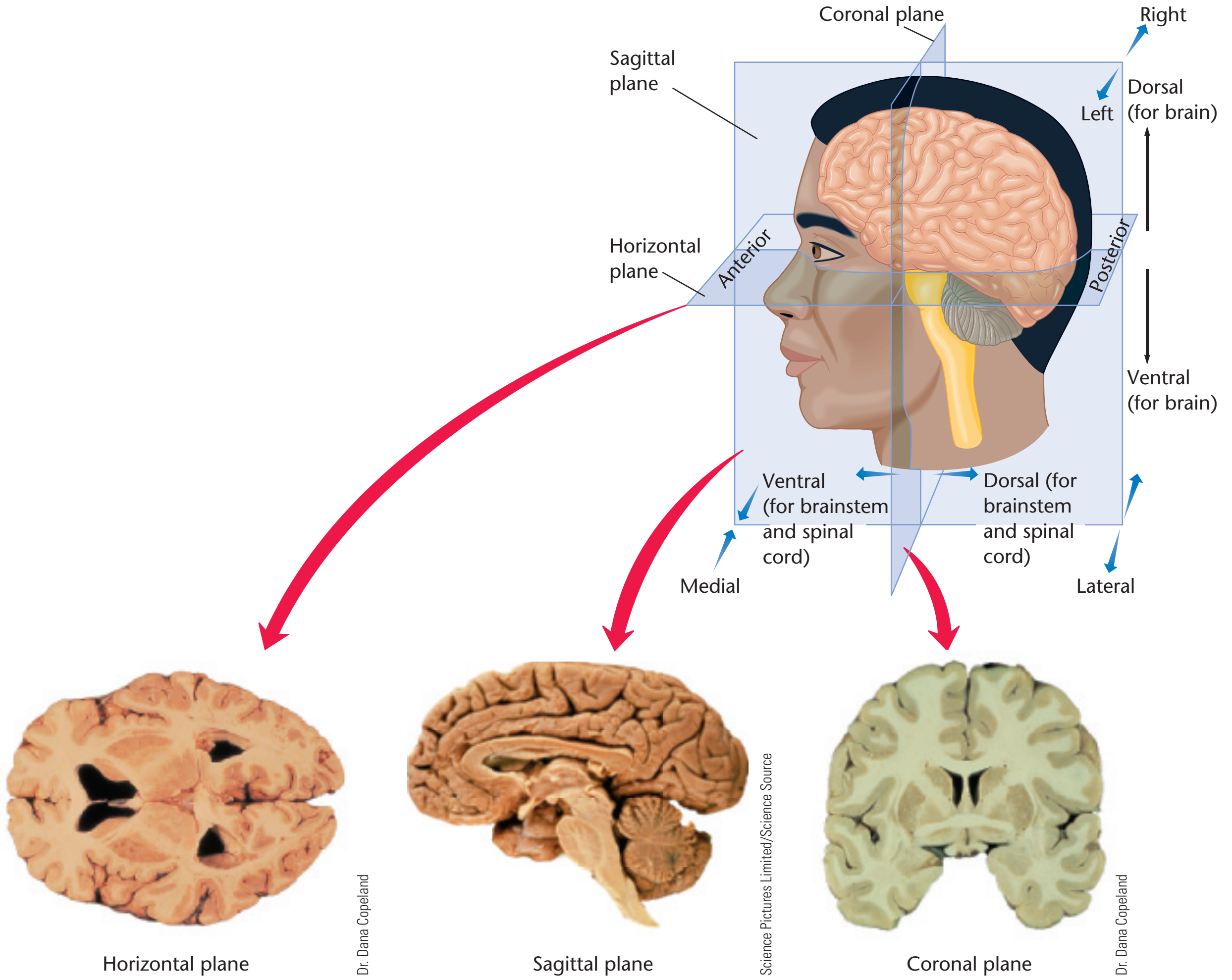
peripheral nervous system (PNS) connects the brain and spinal cord to the rest of the body. Part of the PNS is the **somatic nervous system**, which consists of the axons conveying messages from the sense organs to the CNS and from the CNS to the muscles. Another part of the PNS, the **autonomic nervous system**, controls the body's organs. A special part of the autonomic nervous system is the **enteric nervous system**, which controls the digestive system (Rao and Gershon, 2018).

To follow a map, you must understand *north*, *south*, *east*, and *west.* Because the nervous system is three-dimensional, we need more terms to describe it. As Figure 3.2 and Table 3.1 indicate, **dorsal** means toward the back and **ventral** means toward the stomach. (A *ventri*loquist is literally a "stomach talker.") In a four-legged animal, the top of the brain and spinal cord is dorsal (the side of the animal's back), and the bottom is ventral (the stomach side). The same would be true for you if you crawled on your hands and knees. However, when humans evolved upright posture, the position of the head changed relative to the spinal cord. For convenience, we still apply the terms *dorsal* and *ventral* to the same parts of human anatomy as in other vertebrates. Consequently, the dorsal–ventral axis of the human brain is at a right angle to the dorsal–ventral axis of the spinal cord. Figure 3.2 also illustrates the three ways of taking a plane through the brain, known as horizontal, sagittal, and coronal (or frontal).

Table 3.2 introduces additional terms that are worth learning. Tables 3.1 and 3.2 require careful study and review. After you think you have mastered the terms, check yourself with the following "Stop & Check" questions.

Figure 3.2 Terms for anatomical directions in the nervous system

In four-legged animals, the dorsal and ventral axes for the head are parallel to those for the rest of the body. However, humans' upright posture has tilted the head, so the dorsal and ventral directions of the head are at right angles to those of the spinal cord.



Horizontal plane

Dr. Dana Copeland

Sagittal plane

Science Pictures Limited/Science Source

Coronal plane

Dr. Dana Copeland

Table 3.1 | Anatomical Terms Referring to Directions

Term	Definition
Dorsal	Toward the back, away from the ventral (stomach) side. The top of the human brain is considered dorsal because it has that position in four-legged animals.
Ventral	Toward the stomach, away from the dorsal (back) side
Anterior	Toward the front end
Posterior	Toward the rear end
Superior	Above another part
Inferior	Below another part
Lateral	Toward the side, away from the midline
Medial	Toward the midline, away from the side
Proximal	Located close (approximate) to the point of origin or attachment
Distal	Located more distant from the point of origin or attachment
Ipsilateral	On the same side of the body (e.g., two parts on the left or two on the right)
Contralateral	On the opposite side of the body (one on the left and one on the right)
Coronal plane (or frontal plane)	A plane that shows brain structures as seen from the front
Sagittal plane	A plane that shows brain structures as seen from the side
Horizontal plane (or transverse plane)	A plane that shows brain structures as seen from above

Stop & Check

1. What does *ventral* mean, and what is its opposite?
2. What term means *toward the midline*, and what is its opposite?
3. If two structures are both on the left side of the body, they are _______ to each other. If one is on the left and the other is on the right, they are _______ to each other.
4. The bulges in the cerebral cortex are called _______. The grooves between them are called _______.

See page 79 for the answer.

The Spinal Cord

The **spinal cord** is the part of the CNS within the spinal column. The spinal cord communicates with all the sense organs and muscles except those of the head. It is a segmented structure, and each segment has on both its left and right sides a sensory nerve and a motor nerve, as Figure 3.3 illustrates. One of the earliest discoveries about the functions of the nervous system was that the entering dorsal roots (axon bundles) carry sensory information, and the exiting ventral roots carry motor information. The cell bodies of the sensory neurons are in clusters of neurons outside the spinal cord, called the **dorsal root ganglia**. (*Ganglia* is the plural of *ganglion*, a cluster of neurons. In most cases, a neuron cluster outside the CNS is called a ganglion, and a cluster inside the CNS is called a nucleus.) Cell bodies of the motor neurons are inside the spinal cord.

Table 3.2 | Terms Referring to Parts of the Nervous System

Term	Definition
Lamina	A row or layer of cell bodies separated from other cell bodies by a layer of axons and dendrites
Column	A set of cells perpendicular to the surface of the cortex, with similar properties
Tract	A set of axons within the CNS, also known as a *projection*. If axons extend from cell bodies in structure A to synapses onto B, we say that the fibers “project” from A onto B.
Nerve	A set of axons in the periphery, either from the CNS to a muscle or gland or from a sensory organ to the CNS
Nucleus	A cluster of neuron cell bodies within the CNS
Ganglion	A cluster of neuron cell bodies, usually outside the CNS (as in the sympathetic nervous system)
Gyrus (pl.: gyri)	A protuberance on the surface of the brain
Sulcus (pl.: sulci)	A fold or groove that separates one gyrus from another
Fissure	A long, deep sulcus

Figure 3.3 Diagram of a cross section through the spinal cord

The dorsal root on each side conveys sensory information to the spinal cord; the ventral root conveys motor commands to the muscles.

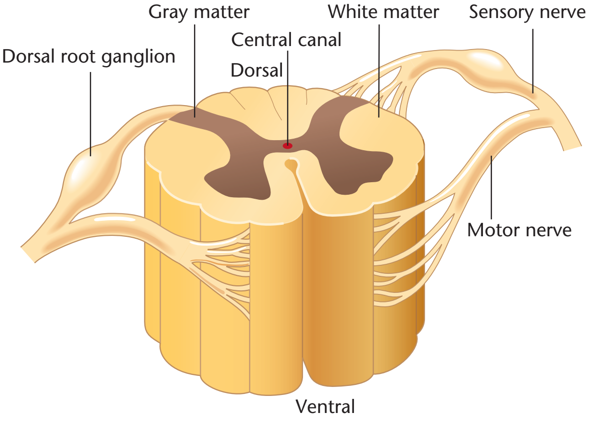


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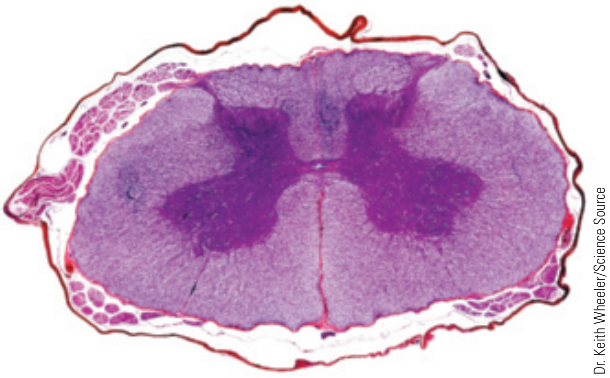
Figure 3.4 Photo of a cross section through the spinal cord

The H-shaped structure in the center is gray matter, composed largely of cell bodies. The surrounding white matter consists of axons.



Dr. Keith Wheeler/Science Source

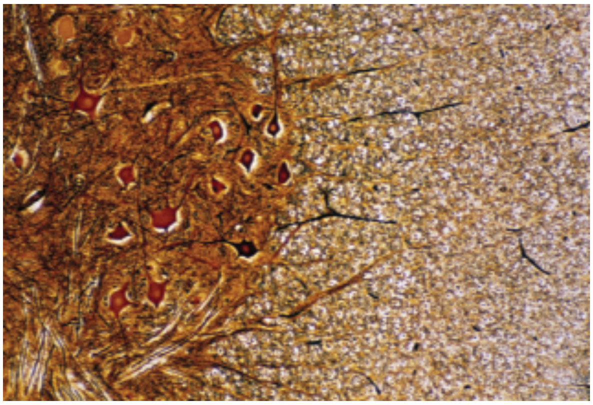
(**Source:** Manfred Kage/Peter Arnold, Inc.)

In the cross sections through the spinal cord depicted in Figures 3.3 and 3.4, the H-shaped **gray matter** in the center of the cord is densely packed with cell bodies and dendrites. Many neurons from the gray matter of the spinal cord send axons to the brain or to other parts of the spinal cord through the **white matter**, containing myelinated axons. Figure 3.5 depicts a close-up view of gray matter and white matter.

Each segment of the spinal cord sends sensory information to the brain and receives motor commands from the brain. All that information passes through tracts of axons in the spinal cord. If the spinal cord is cut at a given segment, the brain loses sensation from that segment and below. The brain also loses motor control over all parts of the body served by that segment and the lower ones.

Figure 3.5 A section of gray matter of the spinal cord (left) and white matter surrounding it

Cell bodies and dendrites reside in the gray matter. Axons travel from one area of gray matter to another in the white matter.



Ed Reschke/Photolibrary/Getty Images

(**Source:** Manfred Kage/Peter Arnold, Inc.)

The Autonomic Nervous System

The autonomic nervous system consists of neurons that receive information from and send commands to the heart, intestines, and other organs. Its two parts are the sympathetic and parasympathetic nervous systems (Figure 3.6). The **sympathetic nervous system**, a network of nerves that prepare the organs for a burst of vigorous activity, consists of chains of ganglia just to the left and right of the spinal cord's central regions (the thoracic and lumbar areas). These ganglia have connections back and forth with the spinal cord. Sympathetic axons prepare the organs for "fight or flight," such as by increasing breathing and heart rate and decreasing digestive activity. Because the sympathetic ganglia are closely linked, they often act as a single system "in sympathy" with one another, although certain events activate some parts more than others. The sweat glands, adrenal glands, muscles that constrict blood vessels, and muscles that erect the hairs of the skin have sympathetic input but no parasympathetic input.

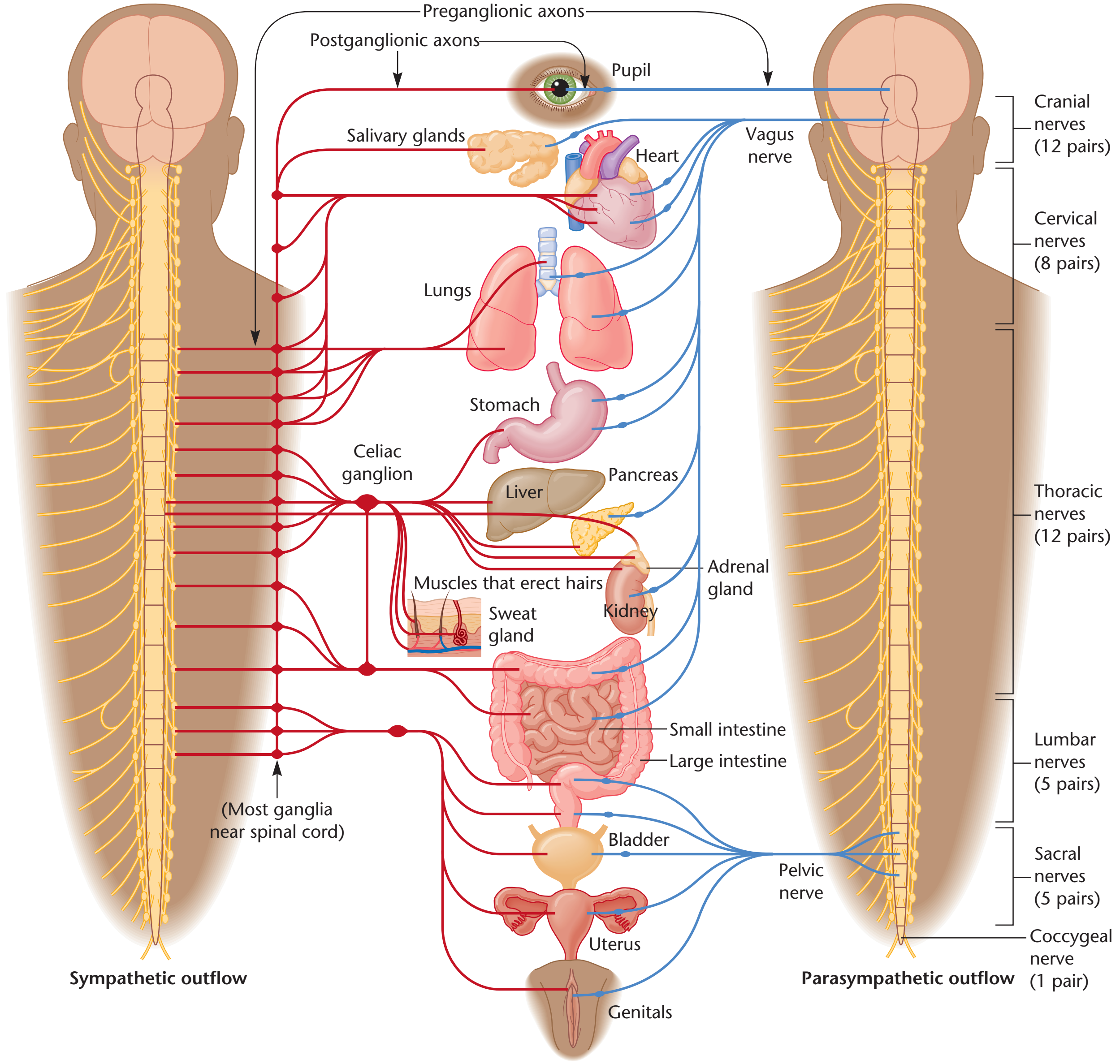
The **parasympathetic nervous system**, sometimes called the "rest and digest" system, facilitates vegetative, nonemergency responses. The term *para* means "beside" or "related to," and parasympathetic activities are related to, and generally the opposite of, sympathetic activities. For example, the sympathetic nervous system increases heart rate, and the parasympathetic nervous system decreases it. The parasympathetic nervous system increases digestive activity, whereas the sympathetic nervous system decreases it. The parasympathetic system also promotes sexual arousal, including erection in males. Although the sympathetic and parasympathetic systems produce contrary effects, both are constantly active to varying degrees, and many stimuli arouse parts of both systems.

The parasympathetic nervous system is also known as the craniosacral system because it consists of the cranial nerves and nerves from the sacral spinal cord (see Figure 3.6). Unlike the ganglia in the sympathetic system, the parasympathetic ganglia are not arranged in a chain near the spinal cord. Rather, long *preganglionic* axons extend from the spinal cord to parasympathetic ganglia close to each organ. Shorter *postganglionic* fibers then extend from the parasympathetic ganglia into the organs themselves. Because the parasympathetic ganglia are not linked to one another, they act more independently than the sympathetic ganglia do. Parasympathetic activity decreases heart rate, increases digestive rate, and, in general, conserves energy.

The parasympathetic nervous system's axons release the neurotransmitter acetylcholine onto the organs. Most sympathetic nervous system axons release norepinephrine, although a few, such as those onto the sweat glands, use acetylcholine. Because the two systems use different transmitters, certain drugs excite or inhibit one system or the other. For example, over-the-counter cold remedies exert most of their effects by blocking parasympathetic activity

Figure 3.6 The sympathetic nervous system (red lines) and parasympathetic nervous system (blue lines)

Note that the adrenal glands, sweat glands, and hair erector muscles receive sympathetic input only.



Preganglionic axons
Postganglionic axons
Pupil
Salivary glands
Heart
Vagus nerve
Cranial nerves (12 pairs)
Cervical nerves (8 pairs)
Lungs
Stomach
Celiac ganglion
Liver
Pancreas
Thoracic nerves (12 pairs)
Adrenal gland
Muscles that erect hairs
Sweat gland
Kidney
Small intestine
Large intestine
Lumbar nerves (5 pairs)
(Most ganglia near spinal cord)
Bladder
Pelvic nerve
Sacral nerves (5 pairs)
Uterus
Coccygeal nerve (1 pair)
Sympathetic outflow
Parasympathetic outflow
Genitals

(**Source:** Starr and Taggart, 1989)

or by increasing sympathetic activity. Because the flow of sinus fluids is a parasympathetic response, drugs that block the parasympathetic system inhibit sinus flow. The side effects of cold remedies stem from their pro-sympathetic, anti-parasympathetic activities: They increase heart rate, blood pressure, and arousal. They inhibit salivation and digestion. Certain decongestant pills containing pseudoephedrine have been withdrawn or restricted because of their potential for abuse.

Stop & Check

5. Motor nerves leave from which side of the spinal cord, dorsal or ventral?
6. Which functions are controlled by the sympathetic nervous system? Which are controlled by the parasympathetic nervous system?

See page 79 for the answer.

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The Hindbrain

The brain has three major divisions: hindbrain, midbrain, and forebrain (Figure 3.7 and Table 3.3). Some neuroscientists prefer terms with Greek roots: rhombencephalon (hindbrain), mesencephalon (midbrain), and prosencephalon (forebrain). You may encounter these terms in other reading.

The **hindbrain**, the posterior part of the brain, consists of the medulla, the pons, and the cerebellum. The medulla and pons, the midbrain, and certain central structures of the forebrain constitute the **brainstem** (Figure 3.8).

The **medulla**, or medulla oblongata, can be regarded as an enlarged extension of the spinal cord. Just as the lower parts of the body connect to the spinal cord via sensory and motor nerves, the head and the organs connect to the medulla and adjacent areas by 12 pairs of **cranial nerves** (one of each pair on the right side and one on the left), as described in Table 3.4 and Figure 3.9. The size of each cranial nerve varies among species. In elephants, the trigeminal nerve that receives sensations from the face is huge because it innervates the trunk, a highly sensitive structure for elephants (Purkart, 2022). The elephant's trigeminal nerve is thicker than its spinal cord!

Figure 3.7 Major divisions of the vertebrate brain

In a fish brain, as depicted here, the forebrain, midbrain, and hindbrain are clearly visible as separate bulges. In adult mammals, the forebrain grows and surrounds the entire midbrain and part of the hindbrain.

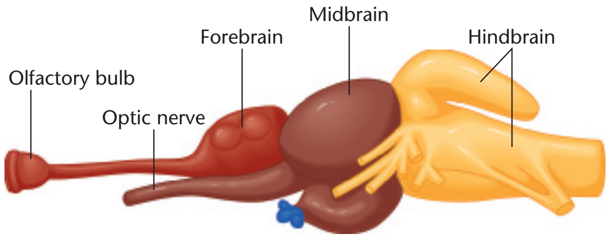
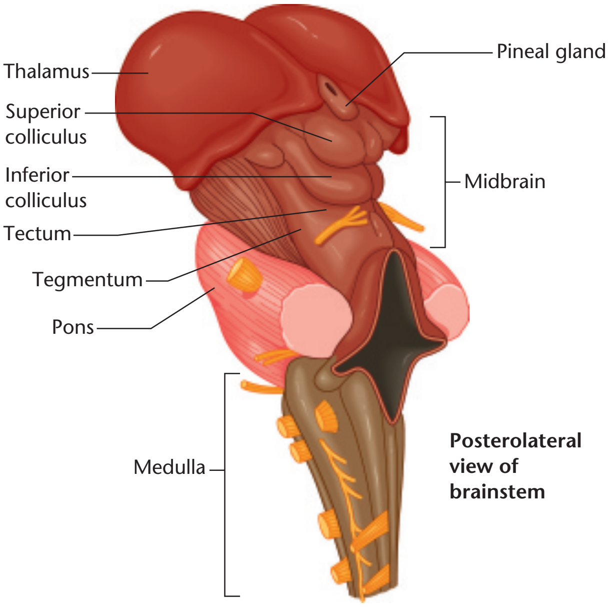


Table 3.3 | Major Divisions of the Vertebrate Brain

Area	Also Known as	Major Structures
Forebrain	Prosencephalon ("forward-brain")	
	Diencephalon ("between-brain")	Thalamus, hypothalamus
	Telencephalon ("end-brain")	Cerebral cortex, hippocampus, basal ganglia
Midbrain	Mesencephalon ("middle-brain")	Tectum, tegmentum, superior colliculus, inferior colliculus, substantia nigra
Hindbrain	Rhombencephalon (literally, "parallelogram-brain")	Medulla, pons, cerebellum

Figure 3.8 The human brainstem

This composite structure extends from the top of the spinal cord into the center of the forebrain. The cerebral cortex surrounds the thalamus, pineal gland, and midbrain.



The cranial nerves originating in the medulla control vital reflexes such as breathing, heart rate, vomiting, salivation, coughing, and sneezing. Because opiate receptors, which suppress activity, are abundant in the medulla, opiates can produce a dangerous decrease in breathing and heart rate.

The **pons** lies anterior and ventral to the medulla. Like the medulla, it contains nuclei for several cranial nerves. The term *pons* is Latin for "bridge," reflecting the fact that in the pons, axons from each half of the brain cross to the opposite side of the spinal cord so that the left hemisphere controls the muscles of the right side of the body and the right hemisphere controls the left side.

The **cerebellum** is a large hindbrain structure with many deep folds. It is one of the first brain areas to start developing and one of the last to complete development (Sathyanesan et al., 2019). The cerebellum has long been known for its contributions to the control of movement, and many older textbooks describe the cerebellum as important for "balance and coordination." True, people with cerebellar damage are clumsy and lose their balance, but the functions of the cerebellum extend far beyond balance and coordination. People with damage to the cerebellum have difficulty with timing, such as judging whether one rhythm is faster than another rhythm. Depending on the location and type of damage, they may have impairments of learning, memory, attention, visual-spatial processing, language, recognizing emotional expressions, or social behavior (De Zeeuw et al., 2021; Ferrari et al., 2018;

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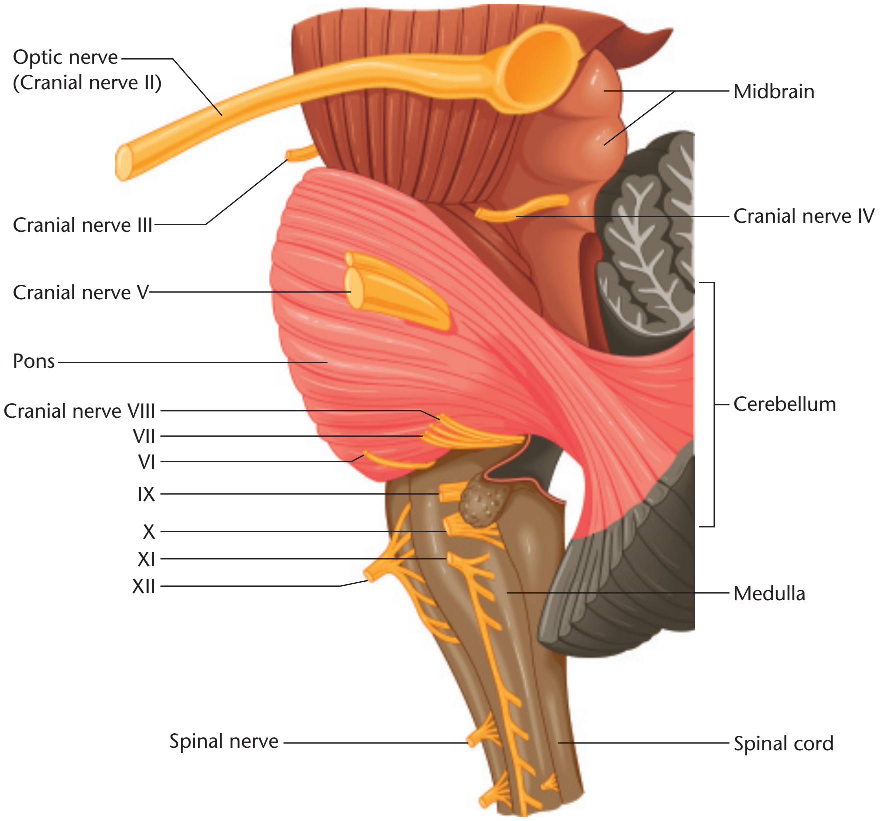
Table 3.4 | The Cranial Nerves

Number and Name	Major Functions
I. Olfactory	Smell
II. Optic	Vision
III. Oculomotor	Control of eye movements; pupil constriction
IV. Trochlear	Control of eye movements
V. Trigeminal	Skin sensations from most of the face; control of jaw muscles for chewing and swallowing
VI. Abducens	Control of eye movements
VII. Facial	Taste from the anterior two-thirds of the tongue; control of facial expressions, crying, salivation, and dilation of the head's blood vessels
VIII. Statoacoustic	Hearing; equilibrium
IX. Glossopharyngeal	Taste and other sensations from throat and posterior one-third of the tongue; control of swallowing, salivation, and throat movements during speech
X. Vagus	Sensations from neck and thorax; control of throat, esophagus, and larynx; parasympathetic nerves to control stomach, intestines, and other organs
XI. Accessory	Control of neck and shoulder movements
XII. Hypoglossal	Control of muscles of the tongue

Cranial nerves III, IV, and VI are coded in red to highlight their similarity: control of eye movements. Cranial nerves VII, IX, and XII are coded in green to highlight their similarity: taste and control of tongue and throat movements. Cranial nerve VII has other important functions as well. Nerve X (not highlighted) also contributes to throat movements, although it is primarily known for other functions.

Figure 3.9 Cranial nerves II through XII

Cranial nerve I, the olfactory nerve, connects directly to the olfactory bulbs of the forebrain.



(**Source:** Based on Braus, 1960)

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Koziol et al., 2014). One hypothesis is that the cerebellum's primary function is to detect sequences of events (Van Overwalle et al., 2020; Vandervert, 2018).

Stop & Check

7. Most of the cranial nerves connect to which brain area?

See page 79 for the answer.

The Midbrain

As the name implies, the **midbrain** is between the hindbrain and the forebrain, although in adult mammals the forebrain surrounds it. The midbrain is more prominent in reptiles, amphibians, and fish. The roof of the midbrain is called the **tectum**. (*Tectum* is the Latin word for "roof." The same root occurs in the geological term *plate tectonics*.) The swellings on each side of the tectum are the **superior colliculus** and the **inferior colliculus** (Figures 3.8 and 3.10). Both are important for sensory processing—the inferior colliculus for hearing and the superior colliculus for vision.

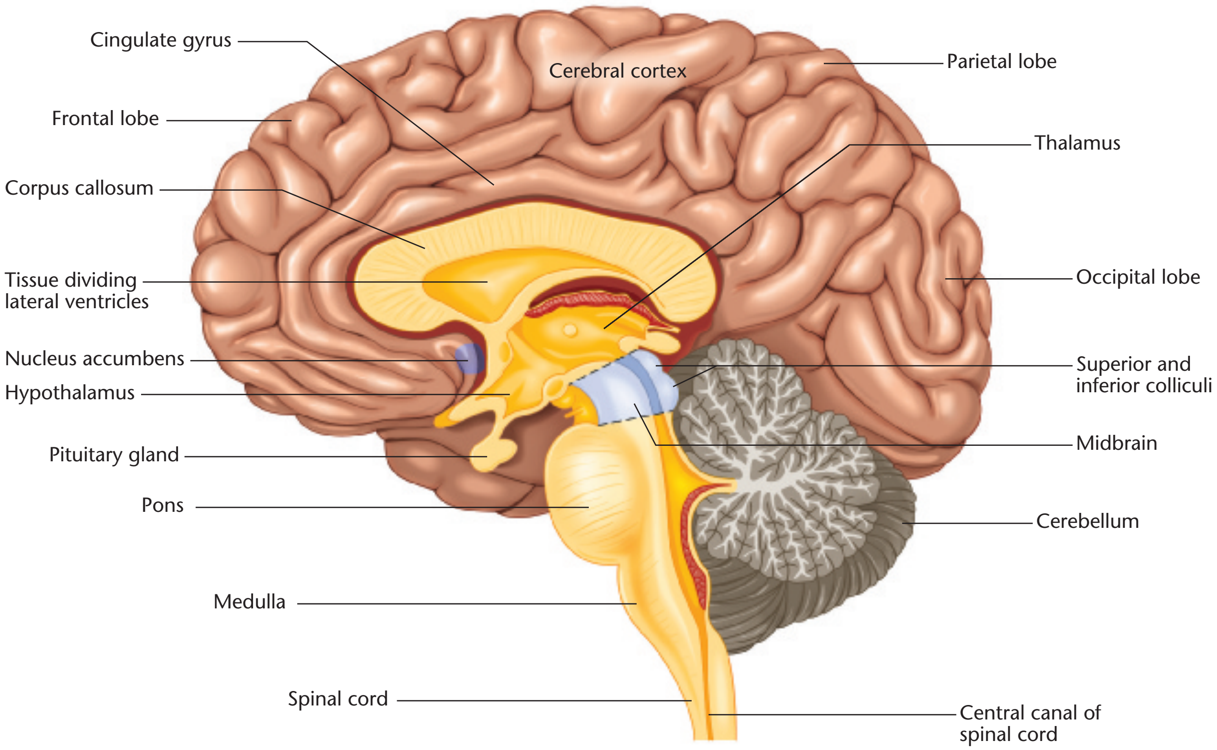
Under the tectum lies the **tegmentum**, the intermediate level of the midbrain. (In Latin, *tegmentum* means a "covering," such as a rug on the floor. The tectum covers the tegmentum, but the tegmentum covers several other midbrain structures.) Another midbrain structure, the **substantia nigra**, gives rise to a dopamine-containing pathway that facilitates readiness for movement.

The Forebrain

The **forebrain**, the most prominent brain area for mammals and birds, consists of two cerebral hemispheres, left and right (Figure 3.11). Each hemisphere is organized to receive sensory information, mostly from the contralateral (opposite) side of the body. It controls muscles, mostly on the contralateral side, by way of axons to the spinal cord and the cranial nerve nuclei.

The outer portion is the cerebral cortex. (*Cerebrum* is a Latin word for "brain." *Cortex* is a Latin word for "bark" or "shell.") Under the cerebral cortex are other structures, including those illustrated in Figure 3.12. The thalamus is the main source of input to the cortex. The hypothalamus is essential for control of eating, drinking, temperature control, and reproductive behaviors. The **amygdala** is part of a circuit that is central for evaluating emotional information, especially with regard to fear. Figure 3.12 shows the positions of these structures in three-dimensional perspective. Figure 3.13 is a coronal (from the front) section through the human brain and a view of the ventral surface of the brain.

Figure 3.10 A sagittal section through the human brain



(**Source:** Based on Nieuwenhuys et al., 1988)

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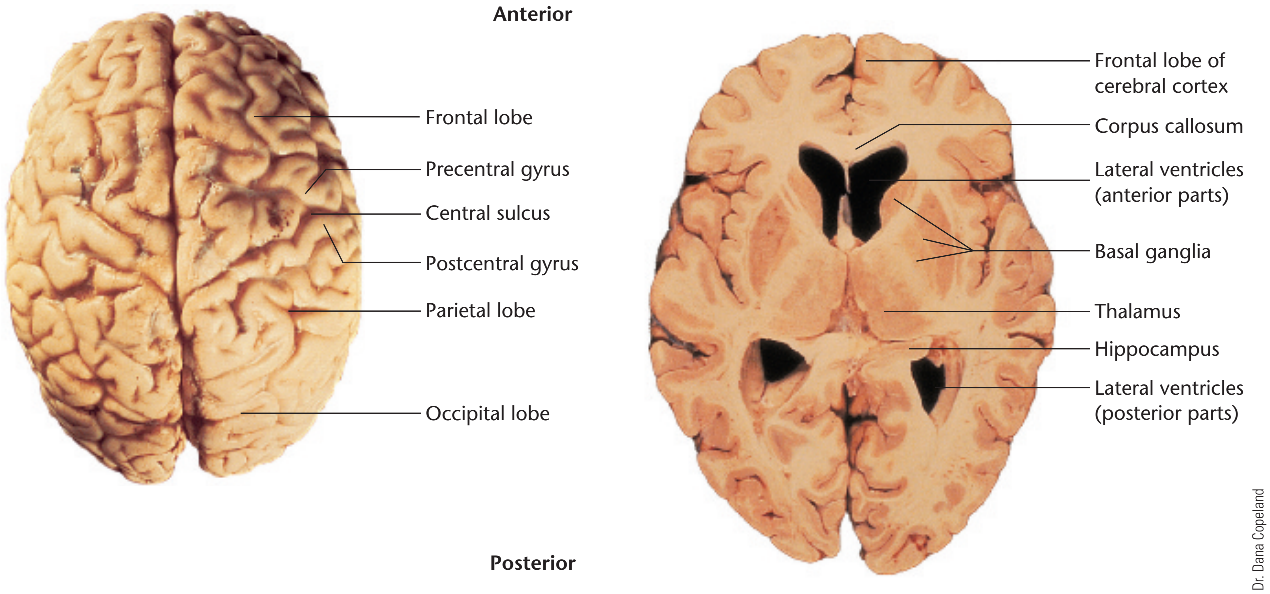
Figure 3.11 Dorsal view of the brain surface and a horizontal section through the brain


Anterior
Frontal lobe
Precentral gyrus
Central sulcus
Postcentral gyrus
Parietal lobe
Occipital lobe
Posterior
Frontal lobe of cerebral cortex
Corpus callosum
Lateral ventricles (anterior parts)
Basal ganglia
Thalamus
Hippocampus
Lateral ventricles (posterior parts)
Dr. Dana Copeland

(**Source:** Photos courtesy of Dr. Dana Copeland)

Figure 3.12 Here, in 3-D perspective, are some important subcortical areas of the human brain.

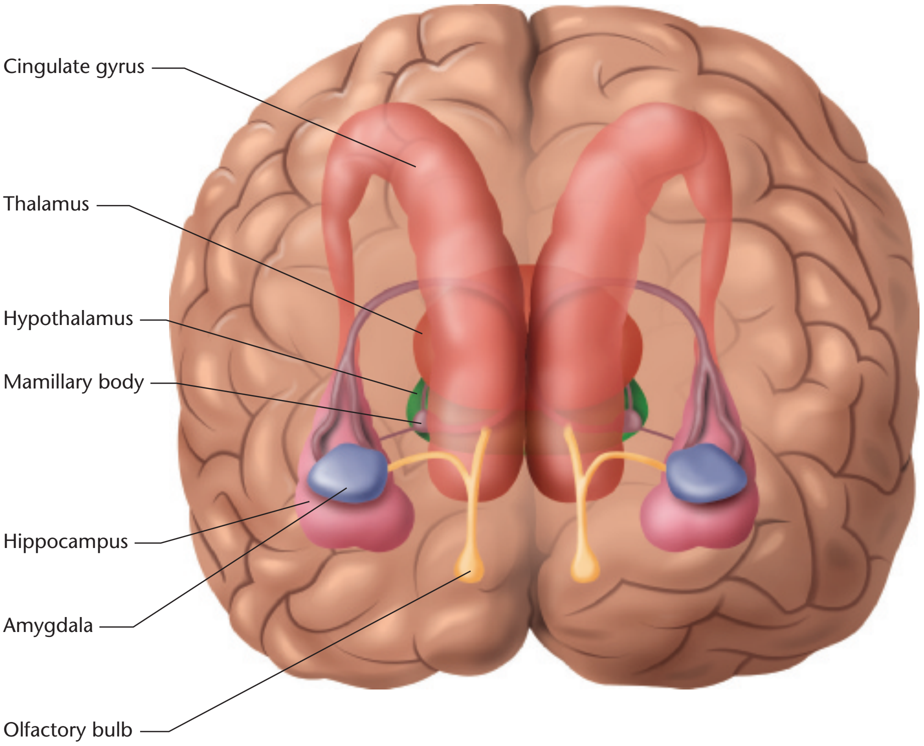
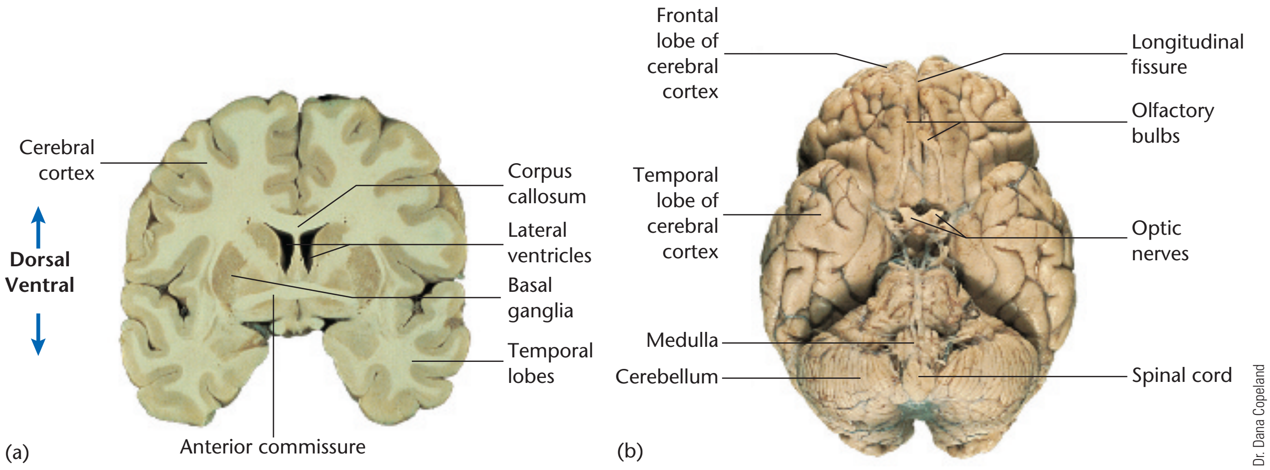

Cingulate gyrus
Thalamus
Hypothalamus
Mamillary body
Hippocampus
Amygdala
Olfactory bulb

Figure 3.13 Two views of the human brain

(a): A coronal section. Note how the corpus callosum and anterior commissure provide communication between the left and right hemispheres.
(b): The ventral surface. The optic nerves (cut here) extend to the eyes.



(**Source:** Photos courtesy of Dr. Dana Copeland)

Thalamus

The **thalamus** is a pair of structures (left and right) in the center of the forebrain. It resembles two small avocados joined side by side. Most sensory information goes first to the thalamus, which processes it and sends output to the cerebral cortex. An exception to this rule is olfactory information, which goes from the olfactory receptors to the olfactory bulbs and then directly to the cerebral cortex.

Many nuclei of the thalamus receive their input from a sensory system, such as vision, process it in various ways, and transmit information to an area of the cerebral cortex, as in Figure 3.14. Another function of the thalamus relates to memory. When you hold information in working memory, activity bounces back and forth between the frontal cortex and the thalamus (Bolkan et al., 2017).

Hypothalamus and Pituitary Gland

The **hypothalamus**, a small area just ventral to the thalamus (Figures 3.10 and 3.12), has widespread connections with the rest of the brain. Damage in the hypothalamus leads to abnormalities in motivated behaviors, such as feeding, drinking, temperature regulation, sexual behavior, or fighting. Because of these important behavioral effects, the small hypothalamus attracts much research attention. Partly through nerves and partly by releasing hormones, the hypothalamus conveys messages to the **pituitary gland**, altering its release of hormones (Figure 3.10).

Basal Ganglia

The **basal ganglia**, a group of subcortical structures lateral to the thalamus, include the caudate nucleus, the putamen, and the globus pallidus (Figure 3.15). Many authorities include other structures as well, especially the nucleus accumbens.

It has long been known that damage to the basal ganglia impairs movement, as in conditions such as Parkinson's disease and Huntington's disease. The basal ganglia integrate motivational and emotional behavior to increase the vigor of selected actions. However, the role of the basal ganglia extends beyond movement. They are critical for gradual learning of skills and habits.

Basal Forebrain

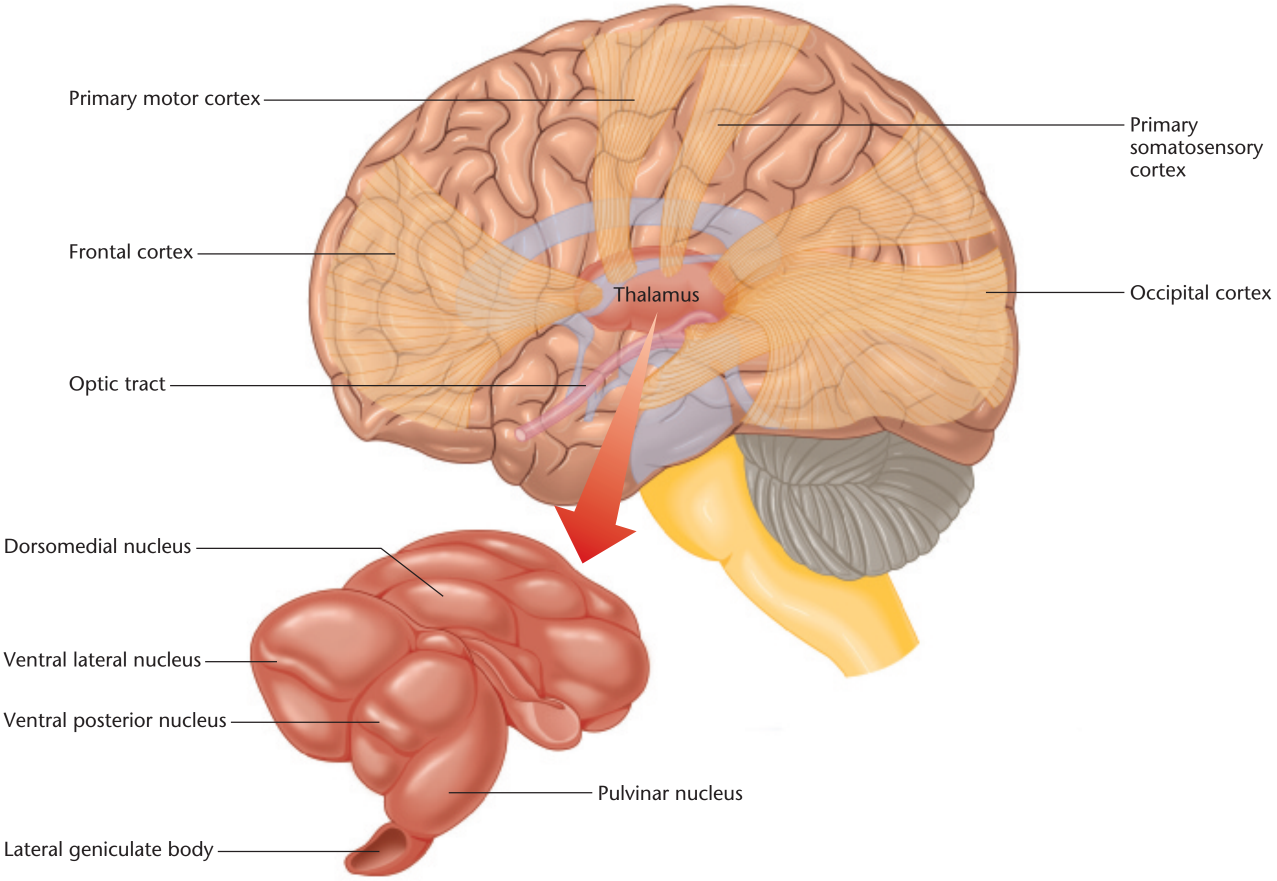
A structure on the ventral surface of the forebrain, the **nucleus basalis**, receives input from the hypothalamus and basal ganglia and sends axons that release acetylcholine to widespread areas in the cerebral cortex (Figure 3.16). The nucleus basalis is a key system for arousal, wakefulness, and attention. Patients with Parkinson's disease and Alzheimer's disease have impairments of attention and intellect because of inactivity or deterioration in the nucleus basalis.

Hippocampus

The **hippocampus** (from the Latin word meaning "sea horse") is a large structure between the thalamus and the cerebral cortex, mostly toward the posterior of the forebrain, as illustrated in Figure 3.12. We consider the hippocampus in more detail in the chapter on memory. The gist of that discussion is that the hippocampus is critical for memories, especially memories for individual events. It is also essential for monitoring where you are and where you are going.

Figure 3.14 Routes of information from the thalamus to the cerebral cortex

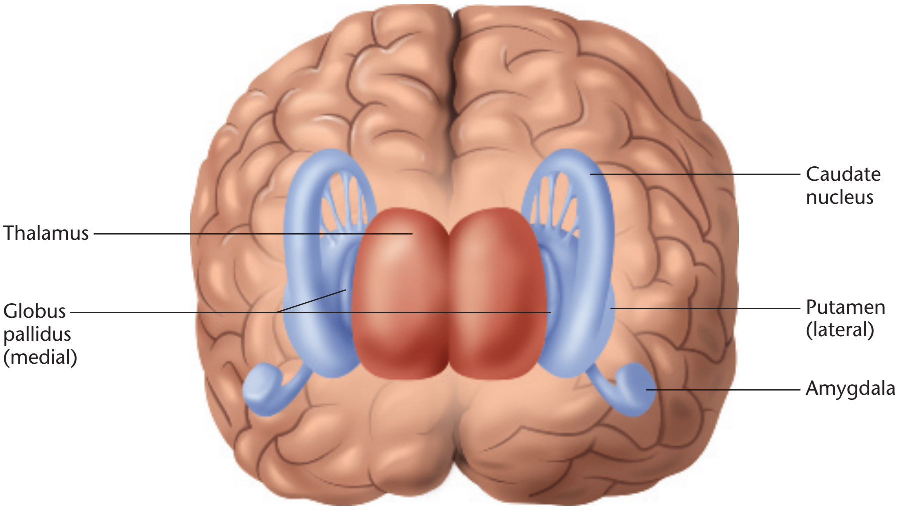
Each thalamic nucleus projects its axons to a different part of the cortex.


Primary motor cortex
Primary somatosensory cortex
Frontal cortex
Thalamus
Occipital cortex
Optic tract
Dorsomedial nucleus
Ventral lateral nucleus
Ventral posterior nucleus
Pulvinar nucleus
Lateral geniculate body

(**Source:** After Nieuwenhuys et al., 1988)

Figure 3.15 The basal ganglia

The thalamus is in the center, the basal ganglia are lateral to it, and the cerebral cortex is on the outside.


Caudate nucleus
Thalamus
Globus pallidus (medial)
Putamen (lateral)
Amygdala

(**Source:** Based on Nieuwenhuys et al., 1988)

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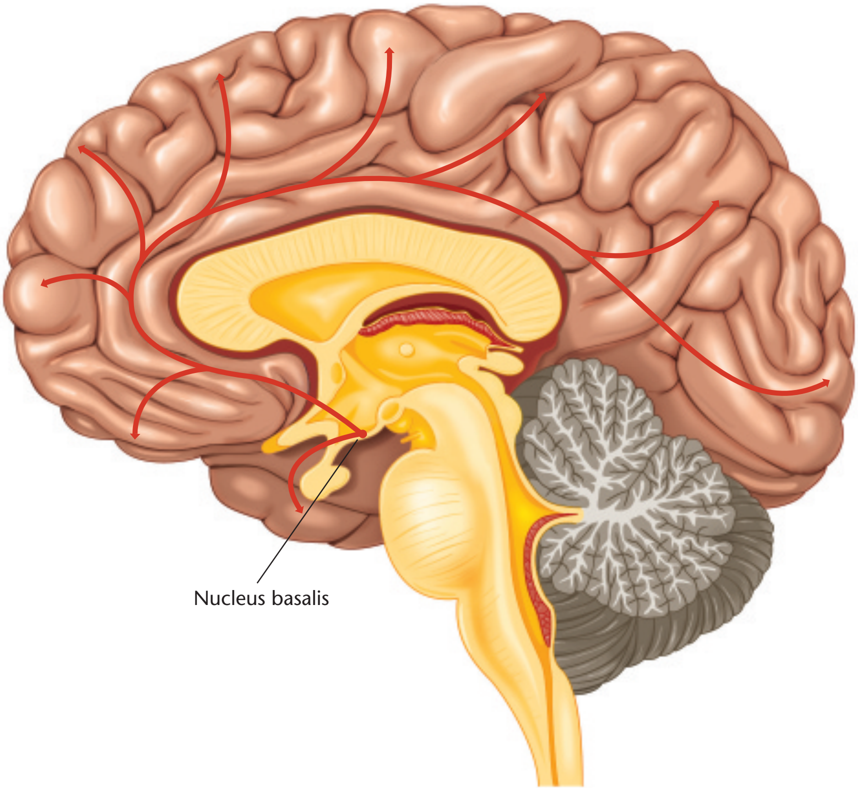
Figure 3.16 The basal forebrain

The nucleus basalis and surrounding areas send axons throughout the cortex, increasing arousal and wakefulness through release of the neurotransmitter acetylcholine.



(**Source:** Based on Woolf, 1991)

Stop & Check

8. Of the following, which are in the hindbrain, which in the midbrain, and which in the forebrain: basal ganglia, cerebellum, hippocampus, hypothalamus, medulla, pituitary gland, pons, substantia nigra, superior and inferior colliculi, tectum, tegmentum, thalamus?
9. Which area provides most of the input to the cerebral cortex?

See page 79 for the answer.

The Ventricles

The nervous system begins its development as a tube surrounding a fluid canal. The canal persists into adulthood as the central canal in the center of the spinal cord, and as the **ventricles**, four fluid-filled cavities within the brain. Each hemisphere contains one of the two large lateral ventricles (Figure 3.17). Toward their posterior, they connect to the third ventricle, positioned at the midline, separating the left and right thalamus. The third ventricle connects to the fourth ventricle in the center of the medulla.

Cells called the *choroid plexus* along the walls of the four ventricles produce **cerebrospinal fluid (CSF)**, a clear fluid similar to blood plasma. CSF flows from the lateral ventricles to the third and fourth ventricles, and then into the central canal of the spinal cord and the narrow spaces between the brain and the **meninges**, membranes that surround the brain and spinal cord. Although the brain has no pain receptors, the meninges do, and meningitis—inflammation of the meninges—is painful. Swollen blood vessels in the meninges produce the pain of a migraine headache (Hargreaves, 2007).

Cerebrospinal fluid cushions the brain against mechanical shock when the head moves. It also provides buoyancy. Just as a person weighs less in water than on land, cerebrospinal fluid helps support the weight of the brain. It also provides a reservoir of hormones and nutrition for the brain and spinal cord.

If the flow of CSF is obstructed, it accumulates in the ventricles or in the space between brain and meninges, increasing pressure on the brain. When this occurs in infants, the skull bones spread, causing an overgrown head. This condition, known as *hydrocephalus* (HI-dro-SEFF-ah-luss), can impair cognitive development, although the results vary from one person to another.

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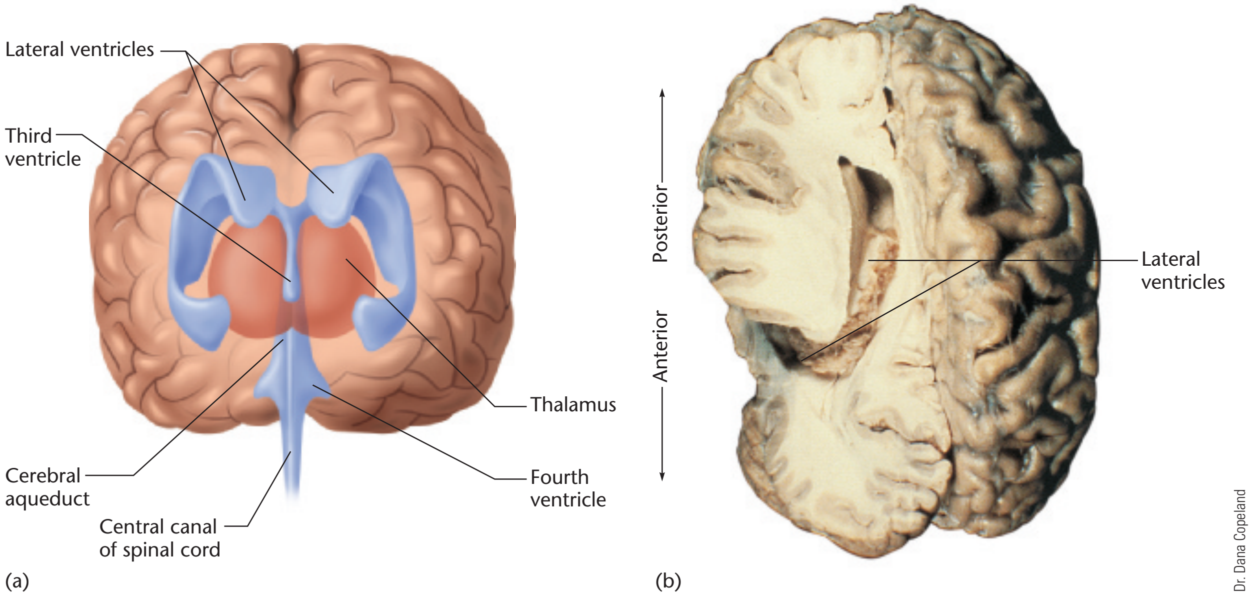
Figure 3.17 The cerebral ventricles

(a) Diagram depicting positions of the four ventricles. (b) Photo of a human brain, viewed from above, with a horizontal cut through one hemisphere to show the position of the lateral ventricles.



(**Source:** Photo courtesy of Dr. Dana Copeland)

Module 3.1 | In Closing

Learning Neuroanatomy

The brain is a complex structure. It will help if you return to review this module as you encounter structures again in later chapters. Gradually, the material will become more familiar.

Summary

1. The vertebrate nervous system has two main divisions, the central nervous system and the peripheral nervous system. **66**
2. Each segment of the spinal cord has a sensory nerve and a motor nerve on both the left and right sides. Spinal pathways convey information to the brain. **68**
3. The sympathetic nervous system (one of the two divisions of the autonomic nervous system) activates the body's internal organs for vigorous activities. The parasympathetic system (the other division) promotes digestion and other nonemergency processes. **69**
4. The central nervous system consists of the spinal cord, hindbrain, midbrain, and forebrain. **71**
5. The hindbrain consists of the medulla, pons, and cerebellum. The medulla and pons control breathing, heart rate, and other vital functions through the cranial nerves. The cerebellum contributes to movement, timing, certain types of learning and conditioning, and detecting sequences of events. **71**
6. The cerebral cortex receives its sensory information, except for olfaction, from the thalamus. Connections between the cortex and the thalamus maintain information in working memory. **73**
7. The subcortical areas of the forebrain include the thalamus, hypothalamus, pituitary gland, basal ganglia, and hippocampus. **73**
8. The cerebral ventricles contain fluid that provides buoyancy and cushioning for the brain. **77**

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Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary, at the end of this book.

amygdala	**73**
autonomic nervous system	**67**
basal ganglia	**75**
brainstem	**71**
central nervous system (CNS)	**66**
cerebellum	**71**
cerebrospinal fluid (CSF)	**77**
cranial nerves	**71**
dorsal	**67**
dorsal root ganglia	**68**
enteric nervous system	**67**
forebrain	**73**
gray matter	**69**
hindbrain	**71**
hippocampus	**75**
hypothalamus	**75**
inferior colliculus	**73**
medulla	**71**
meninges	**77**
midbrain	**73**
neuroanatomy	**65**
nucleus basalis	**75**
parasympathetic nervous system	**69**
peripheral nervous system (PNS)	**67**
pituitary gland	**75**
pons	**71**
somatic nervous system	**67**
spinal cord	**68**
substantia nigra	**73**
superior colliculus	**73**
sympathetic nervous system	**69**
tectum	**73**
tegmentum	**73**
thalamus	**75**
ventral	**67**
ventricles	**77**
white matter	**69**

Thought Question

Being nervous may interfere with sexual arousal. Explain why, with reference to the sympathetic and parasympathetic nervous systems.

Stop & Check Answers

1. Ventral means toward the stomach side. Its opposite is dorsal.
2. Medial; lateral
3. Ipsilateral; contralateral
4. Gyri; sulci. To remember sulcus, think of the word *sulk*, meaning "to pout" (and therefore lie low).
5. Ventral.
6. The sympathetic nervous system prepares the organs for vigorous fight-or-flight activity. The parasympathetic system increases vegetative responses such as digestion.
7. The medulla and pons.
8. Hindbrain: cerebellum, medulla, and pons. Midbrain: substantia nigra, superior and inferior colliculi, tectum, and tegmentum. Forebrain: basal ganglia, hippocampus, hypothalamus, pituitary, and thalamus.
9. Thalamus

Module 3.1 | End-of-Module Quiz

1. What does *dorsal* mean?
   - **a.** Toward the side
   - **b.** Toward the back
   - **c.** Toward the stomach
   - **d.** Toward the head

2. If one structure is on the left and another is on the right, what is their relationship?
   - **a.** Medial
   - **b.** Ventral
   - **c.** Ipsilateral
   - **d.** Contralateral

3. What is a *gyrus* in the brain?
   - **a.** A bulge in the cortex
   - **b.** A fluid-filled cavity
   - **c.** An indentation
   - **d.** A bundle of axons

4. What is the function of the ventral roots of the spinal cord?
   - **a.** They receive sensory input.
   - **b.** They control motor output.
   - **c.** They convey information from the brain to the spinal cord.
   - **d.** They convey information from the spinal cord to the brain.

5. The side effects of most cold remedies demonstrate the effects of what?
    - **a.** The ventricles
    - **b.** The enteric nervous system
    - **c.** The meninges
    - **d.** The sympathetic nervous system

6. Which of these controls breathing, heart rate, and salivation?
    - **a.** The hippocampus
    - **b.** The cranial nerves
    - **c.** The basal ganglia
    - **d.** The pituitary gland

7. Which of these is part of the forebrain?
    - **a.** Hippocampus
    - **b.** Medulla
    - **c.** Pons
    - **d.** Cerebellum

8. What sensation reaches the cerebral cortex without passing through the thalamus?
    - **a.** Olfaction
    - **b.** Vision
    - **c.** Pain
    - **d.** Hearing

9. Which brain area controls the secretions from the pituitary gland?
    - **a.** Medulla
    - **b.** Hippocampus
    - **c.** Hypothalamus
    - **d.** Basal ganglia

10. What do the ventricles contain?
    - **a.** Densely packed neuron cell bodies
    - **b.** Glia
    - **c.** Cerebrospinal fluid
    - **d.** Long axons

Answers: 1b, 2d, 3a, 4b, 5d, 6b, 7a, 8a, 9c, 10c.

Module 3.2

The Cerebral Cortex

Learning Objectives

After studying this module, you should be able to:

5. Distinguish between the laminae and columns of the cortex.
6. List the four lobes of the cerebral cortex and describe their principal functions.
7. Describe the binding problem and explain its theoretical importance.

The largest part of the mammalian brain is the **cerebral cortex**. The cells on the outer surface of the cerebral cortex are gray matter, and their axons extending inward are white matter (Figure 3.13a). Neurons in each hemisphere communicate with the corresponding part of the other hemisphere through two bundles of axons, the **corpus callosum** (Figures 3.10, 3.11, and 3.13) and the smaller **anterior commissure** (Figure 3.13). Several other commissures (pathways across the midline) link subcortical structures.

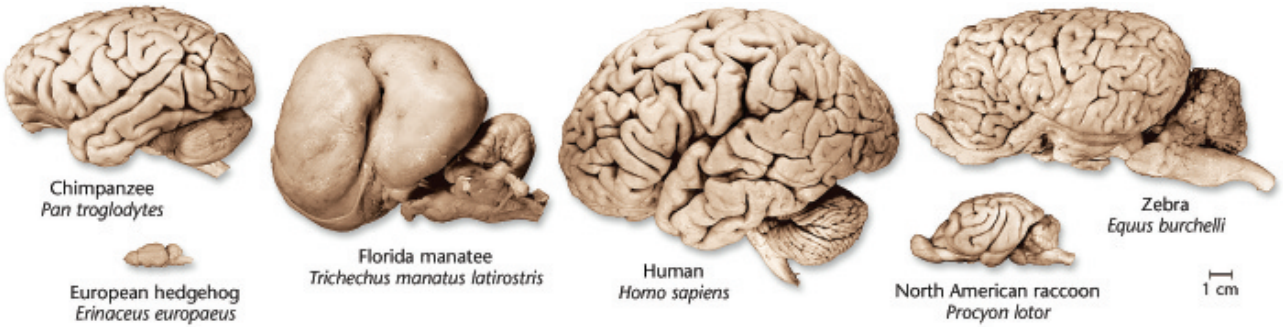
The basic organization of the cerebral cortex is remarkably similar among mammalian species (Harris and Shepherd, 2015). The visual cortex is in the same place, the auditory cortex is in the same place, and so forth. The axon connections are similar also (Assaf et al., 2020). Even the brains of birds are organized similarly to those of mammals (Stacho et al., 2020). However, brains vary enormously in size. The largest mammalian brains are 100,000 times larger than the smallest ones (Herculano-Houzel, 2011).

If we compare mammalian species, we see differences in the size of the cerebral cortex and the degree of folding (Figure 3.18). Compared to other mammals of comparable size, the **primates**—monkeys, apes, and humans—have a larger cerebral cortex, more folding, and more neurons per unit of volume (Herculano-Houzel, 2011). Larger animals, such as elephants, have larger brain size but also larger neurons and fewer neurons per unit of volume. Humans have almost three times as many neurons in the cerebral cortex as elephants have, although the elephant brain is more than twice as large (Herculano-Houzel et al., 2015). In Figure 3.19, the investigators arranged the insectivores and primates from left to right in terms of what percentage of their brain was devoted to the forebrain, including the cerebral cortex (Clark et al., 2001). They also inserted tree shrews, a species often considered intermediate between insectivores and primates. Note that as the proportion devoted to the forebrain increases, the relative sizes of the midbrain and medulla decrease. That is, humans and other primates have a larger than average cerebral cortex, in proportion to the rest of the brain.

Curiously, the cerebellum occupies a nearly constant percentage—about 10 to 14 percent of the brain in nearly

Figure 3.18 Comparison of mammalian brains

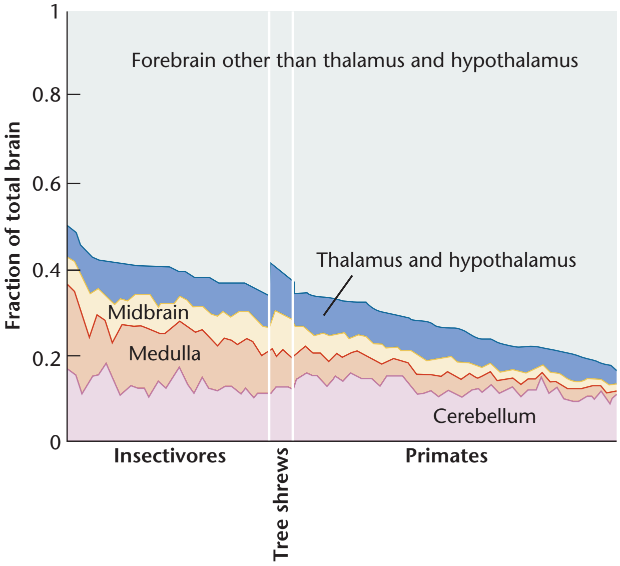
All mammals have the same brain subareas in the same locations.



From the University of Wisconsin-Madison Comparative Mammalian Brain Collection, Wally Welker, Curator. Project supported by the National Science Foundation

Figure 3.19 Relative sizes of five brain components in insectivores and primates

The forebrain composes a larger percentage of primate than insectivore brains. Note also the nearly constant fraction devoted to the cerebellum.



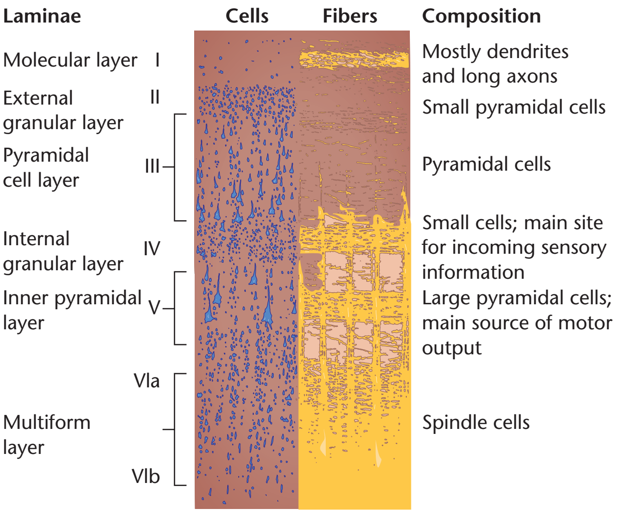
(**Source:** Figure 1, p. 189, from "Scalable architecture in mammalian brains," by D. A. Clark, P. P. Mitra, and S. S-H. Wang, 2001, *Nature, 411*, pp. 189–193. Reprinted with permission from Nature. Copyright © 2001 Macmillan Magazine Limited.)

all species (Herculano-Houzel et al., 2015). Most species have about four (mostly tiny) neurons in the cerebellum for every one in the cerebral cortex (Herculano-Houzel, 2011). Why? Good question. Elephants, however, have a much larger number of neurons in the cerebellum, proportional to the rest of the brain—48 times as many neurons as in the cerebral cortex (Herculano-Houzel et al., 2015). Why? Another good question.

Organization of the Cerebral Cortex

The microscopic structure of neurons varies from one cortical area to another, as does their density per volume (Collins, 2011). In humans and most other mammals, the cerebral cortex contains up to six distinct **laminae**, layers of cell bodies parallel to the surface of the cortex (Figure 3.20). The laminae vary in prominence from one part of the cortex to another, and a given lamina may be absent from certain areas. Lamina IV, which receives sensory information, is prominent in the sensory areas of the cortex but absent from the motor cortex. Lamina V, which sends long axons to the spinal cord, is thickest in the motor cortex. Layer I, with many axons and dendrites but few cells, is a site for many connections, including those that are essential for learning.

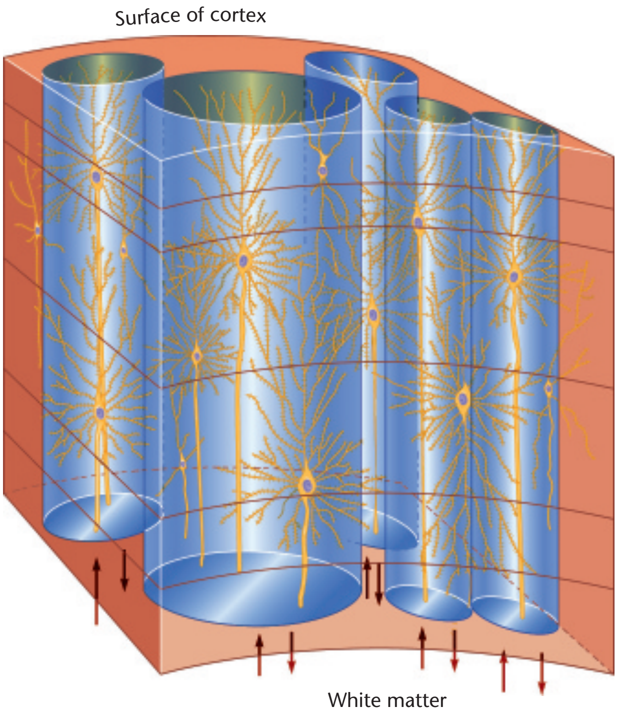
Figure 3.20 The six laminae of the human cerebral cortex


Laminae
Cells
Fibers
Composition
Molecular layer I
Mostly dendrites and long axons
External granular layer II
Small pyramidal cells
Pyramidal cell layer III
Pyramidal cells
Internal granular layer IV
Small cells; main site for incoming sensory information
Inner pyramidal layer V
Large pyramidal cells; main source of motor output
VIa
Multiform layer
VIb
Spindle cells

(**Source:** Adapted from Ranson and Clark, 1959)

Figure 3.21 Columns in the cerebral cortex

Each column extends through several laminae. Neurons within a given column have similar properties. For example, in the somatosensory cortex, all the neurons within a given column respond to stimulation of the same area of skin.


Surface of cortex
White matter

The cells of the cortex are also organized into **columns** of cells perpendicular to the laminae. Figure 3.21 illustrates the idea of columns, although in nature they are not so

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straight. The cells within a column have similar properties to one another. For example, if one cell in a column responds to touch on the palm of the left hand, then the other cells in that column do, too. If one cell responds to a horizontal pattern of light at a particular location, then other cells in the column respond to the same pattern in nearby locations.

Stop & Check

10. Why does the thickness of laminae IV and V vary from one cortical area to another?

See page 89 for the answer.

The Occipital Lobe

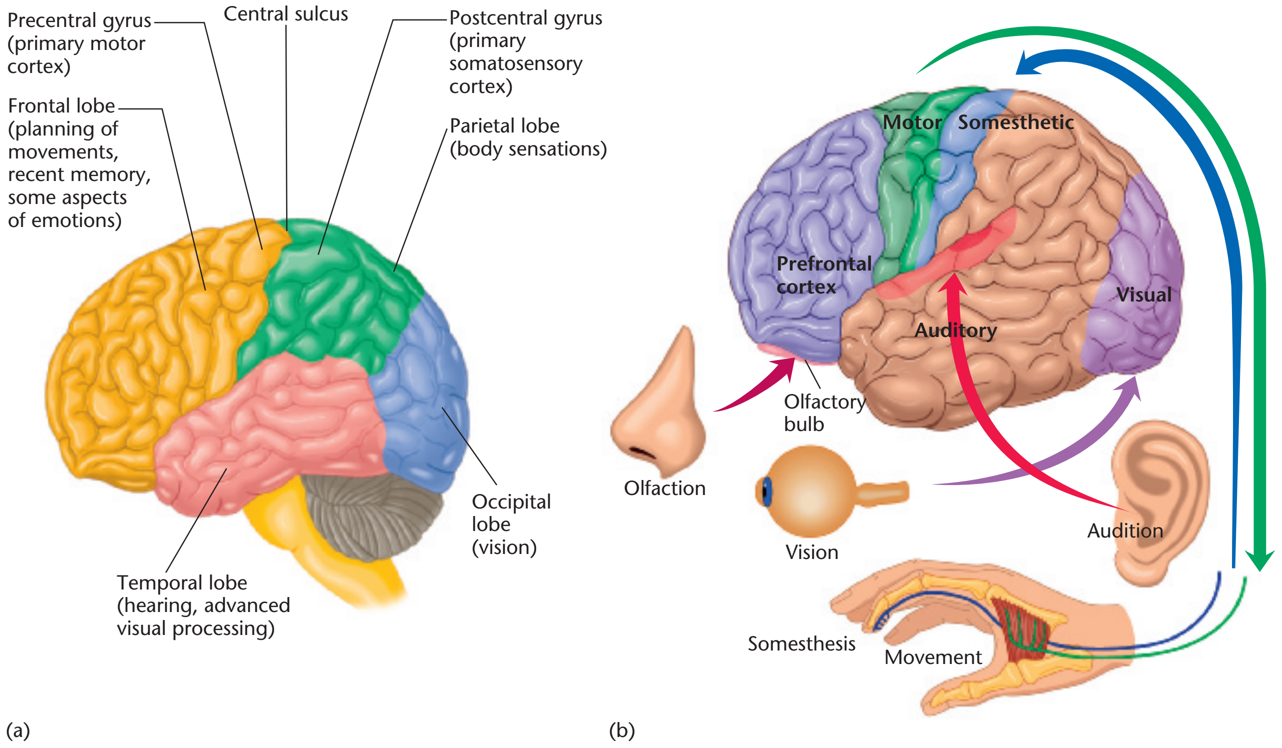
We group the areas of cortex into four *lobes* named for the skull bones that lie over them: occipital, parietal, temporal, and frontal. The **occipital lobe**, at the posterior (caudal) end of the cortex (Figure 3.22), is the main target for visual information. The posterior pole of the occipital lobe is called the *primary visual cortex*, or *striate cortex*, because of its striped appearance in cross section. Damage in the striate cortex causes *cortical blindness* in the related part of the visual field. For example, extensive damage to the striate cortex of the right hemisphere causes blindness in the left visual field (the left side of the world from the viewer's perspective). A person with complete cortical blindness has normal eyes and pupillary reflexes, but no conscious visual perception and no visual imagery (not even in dreams). People who experience eye damage become blind, but if they have an intact occipital cortex and previous visual experience, they can still have visual imagery and visual dreams (Sabo and Kirtley, 1982). In short, the eyes provide the stimulus, and the visual cortex provides the experience.

The Parietal Lobe

The **parietal lobe** lies between the occipital lobe and the **central sulcus**, a deep groove in the surface of the cortex (Figure 3.23). The area just posterior to the central sulcus, the **postcentral gyrus**, or *primary somatosensory cortex*, receives sensations from touch receptors, muscle-stretch receptors, and joint receptors. Brain surgeons sometimes use only local anesthesia, anesthetizing the scalp but leaving the brain awake. If during this process they lightly stimulate the postcentral gyrus, people report tingling sensations on the opposite side of the body.

Figure 3.22 Areas of the human cerebral cortex

(a) The four lobes: occipital, parietal, temporal, and frontal. (b) The primary sensory cortex for vision, hearing, and body sensations; the primary motor cortex; and the olfactory bulb, responsible for the sense of smell.


Precentral gyrus (primary motor cortex)
Central sulcus
Postcentral gyrus (primary somatosensory cortex)
Frontal lobe (planning of movements, recent memory, some aspects of emotions)
Parietal lobe (body sensations)
Occipital lobe (vision)
Temporal lobe (hearing, advanced visual processing)
(a)
Motor
Somesthetic
Prefrontal cortex
Visual
Auditory
Olfactory bulb
Olfaction
Vision
Audition
Somesthesis
Movement
(b)

(**Source:** for part b: Deacon, 1990)

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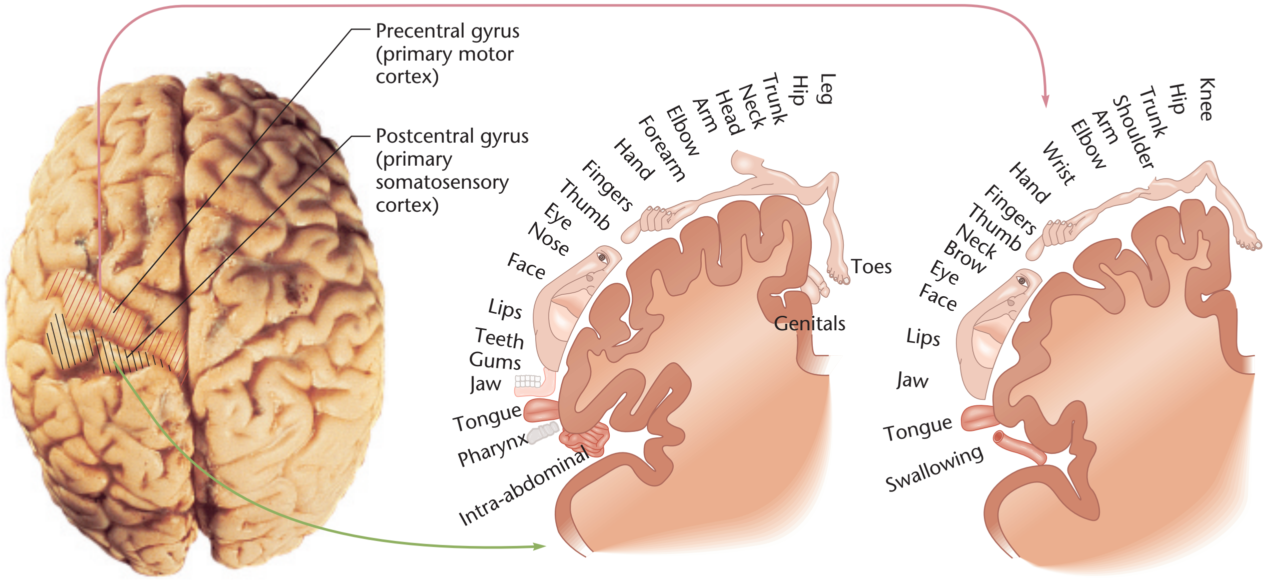
Figure 3.23 Approximate representation of sensory and motor information in the cortex

(a) Each location in the somatosensory cortex represents sensation from a different body part. (b) Each location in the motor cortex regulates movement of a different body part.



(a) Somatosensory cortex

(b) Motor cortex

Dr. Dana Copeland

(**Source:** Based on Penfield and Rasmussen, 1950)

The postcentral gyrus includes four bands of cells parallel to the central sulcus. Separate areas along each band receive simultaneous information from different parts of the body, as illustrated in Figure 3.23a (Nicolelis et al., 1998). Two of the bands receive mostly light-touch information, one receives deep-pressure information, and one receives a combination of both (Kaas et al., 1979). In effect, the postcentral gyrus represents the body four times.

Information about touch and body location is important not only for its own sake but also for interpreting visual and auditory information. For example, if a person sees something in the upper-left portion of the visual field, their brain needs to know in which direction their eyes are turned, the position of their head, and the tilt of their body before it can determine the location of what they see. The parietal lobe monitors the information about eye, head, and body positions and passes it on to brain areas that control movement. The parietal lobe is essential not only for spatial information but also numerical information (Hubbard et al., 2005). That overlap makes sense when you consider all the ways in which numbers relate to space—including the fact that many persons initially use fingers to count.

The Temporal Lobe

The **temporal lobe**, the lateral portion of each hemisphere, near the temples (Figure 3.22), is the primary cortical target for auditory information. The human temporal lobe—mainly the left temporal lobe for most people—is essential for speech. The temporal lobe also contributes to complex aspects of vision, including perception of movement and recognition of faces and other objects. When patients with schizophrenia report hallucinations, brain scans detect activity in the temporal lobes (Dierks et al., 1999). Frequent auditory hallucinations are related to thinner than average auditory cortex in the left temporal lobe (Morch-Johnsen et al., 2017; Roes et al., 2020).

The temporal lobes are also important for emotional and motivational behaviors. Temporal lobe damage can lead to a set of behaviors known as the **Klüver-Bucy syndrome**. The investigators who first described it (Klüver and Bucy, 1939) reported that monkeys failed to display normal fears and anxieties after temporal lobe damage. They put almost anything they find into their mouths and attempt to pick up snakes and lighted matches (which intact monkeys consistently avoid). The monkeys also had maladaptive sexual and eating behaviors, and they explored things by putting them into their mouths, as infants often do. Klüver-Bucy syndrome also occurs occasionally in humans after temporal lobe damage, where the most common symptoms are inappropriate sexual behaviors, overeating, and excessive lip-smacking or other mouth movements (Clay et al., 2019).

The area where the parietal lobe and the temporal lobe meet, close also to the occipital lobe, is the **temporoparietal junction**. It is conveniently located to

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receive input from vision, hearing, and body senses. This area apparently serves multiple functions, including attention, body awareness, and social cognition. Damage or disruption in this area, especially in the right hemisphere, impairs the ability to imagine how something would appear from someone else's perspective (Donaldson et al., 2015; Martin et al., 2020).

The Frontal Lobe

The **frontal lobe**, containing the primary motor cortex and the prefrontal cortex, extends from the central sulcus to the anterior limit of the brain (Figure 3.22). Its posterior portion, the **precentral gyrus**, is specialized for the control of fine movements, such as moving a finger. Each area along that gyrus controls one part of the body, mostly on the contralateral (opposite) side. Figure 3.23b depicts the traditional map of the precentral gyrus, also known as the *primary motor cortex*.

The most anterior portion of the frontal lobe is the **prefrontal cortex**. Species with a larger cerebral cortex devote a larger percentage of it to the prefrontal cortex (Figure 3.24). For example, it occupies almost twice as high a percentage of the human brain as it does of a monkey brain (Donahue et al., 2018).

Several areas in the prefrontal cortex and the temporoparietal junction have come to be known as the **default network**. These are the areas that dominate activity when you don't need to concentrate on anything in particular. They increase their activity when you daydream, when you think about your past or imagine your future, or when you try to make sense of what other people have been saying or doing (Buckner and DiNicola, 2019; Yeshurun et al., 2021). We often assume that daydreaming is unimportant, but it prepares us for decisions we might have to face later. The default network is also active when your brain replays recent experiences, an important process for storing memories (Higgins et al., 2021).

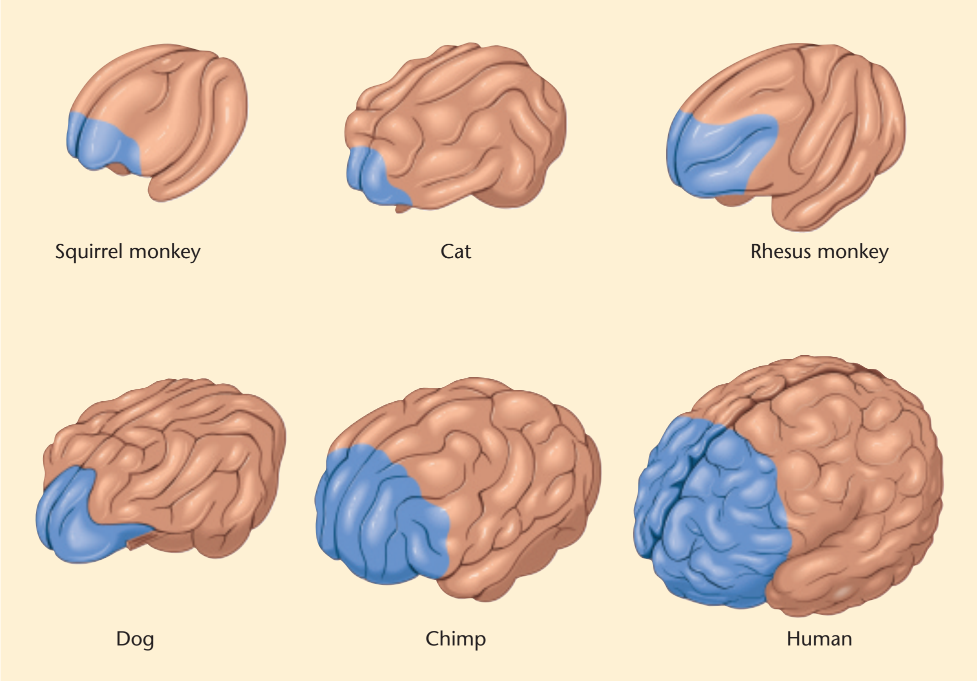
Stop & Check

11. Which lobe of the cerebral cortex includes the primary auditory cortex?
12. Which lobe of the cerebral cortex includes the primary somatosensory cortex?
13. Which lobe of the cerebral cortex includes the primary visual cortex?
14. Which lobe of the cerebral cortex includes the primary motor cortex?

See page 89 for the answer.

Figure 3.24 Species differences in prefrontal cortex

Note that the prefrontal cortex (blue area) constitutes a larger proportion of the human brain than of these other species.



(**Source:** Based on Fuster, 1989)

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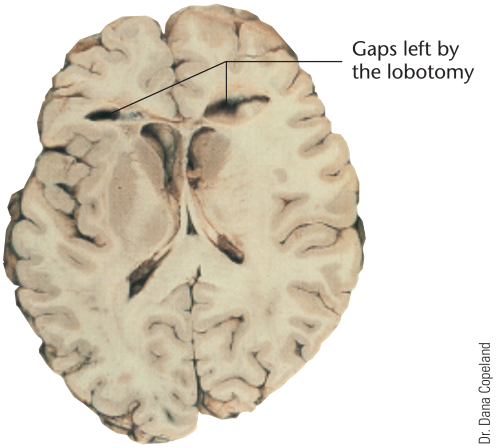
The Rise and Fall of Prefrontal Lobotomies



A horizontal section of the brain of a person who had a prefrontal lobotomy many years earlier. The two holes in the frontal cortex are the visible results of the operation.

You probably have heard of the infamous procedure known as **prefrontal lobotomy**—surgery that consisted of damaging the prefrontal cortex or cutting its connections to the rest of the cortex. Lobotomy began after a report in 1935 that damaging the prefrontal cortex of laboratory primates made them tamer without noticeably impairing their sensations or coordination. A few physicians reasoned loosely—uh, very loosely—that the same operation might help people with severe psychiatric disorders. In their defense, this was a time when psychiatrists had no effective treatment for severe disorders. Practitioners of lobotomy reported benefits for people who were otherwise considered untreatable, and in 1949 the most prominent practitioner, Egaz Moniz, received a Nobel Prize for his work on lobotomy, one of the most embarrassing and regrettable decisions in the history of the prize.

In the late 1940s and early 1950s, at a time when legal and ethical restraints in medicine were lax, about 40,000 prefrontal lobotomies were performed in the United States, many of them by Walter Freeman, a medical doctor untrained in surgery (Shutts, 1982). His techniques were crude, even by the standards of the time, using such instruments as an electric drill and a metal pick. He performed many operations in his office or other nonhospital sites. (Freeman carried his equipment in his car, which he called his "lobotomobile.")

At first, Freeman and others limited the technique to people with severe schizophrenia, for which no effective treatment was available at the time. When the treatment was often ineffective, the surgeons imagined that perhaps it would be more effective in patients who had not already deteriorated so much. Freeman began lobotomizing people with less serious problems, including some people whom we would consider mentally healthy by today's standards. When drug therapies became available in the mid-1950s, lobotomies quickly dropped out of favor.

Among the common consequences of prefrontal lobotomy were apathy, lack of initiative, memory disorders, distractibility, and a loss of emotional expressions (Stuss and Benson, 1984). People with prefrontal damage often acted impulsively because they were unable to calculate adequately the probable outcomes of their behaviors.

Functions of the Prefrontal Cortex

An analysis of thousands of studies concluded that the prefrontal cortex has three major regions (de la Vega et al., 2016). The posterior portion is associated mostly with movement. The middle zone pertains to cognitive control, emotional reactions, and certain aspects of memory. After damage in this area, people can learn that stimulus A is better than B, and that B is better than C, but they might not infer that A is better than C. They form memories, but they often don't apply them to new situations (Spalding et al., 2018).

The anterior zone of the prefrontal cortex is important for making decisions, evaluating which of several courses of action is likely to achieve the best outcome. When you decide whether to do something, you may consider the difficulty of the action, the probabilities of success and failure, and how valuable the possible reward would be to you, all things considered. For example, the chance to win a pizza becomes less valuable if you have just finished a meal. An opportunity to win a few extra-credit points is valuable if you think you are on the borderline between two grades, but less valuable otherwise. If you have a choice between spending money now and saving it for later, you try to compare the possibility of current pleasure and the possible need for money later. Cells in the prefrontal cortex respond to these complex factors (Hunt et al., 2012; Wallis, 2012). People with prefrontal cortical damage often make decisions that seem impulsive, because they have difficulty weighing all the likely pros and cons.

Stop & Check

15. What are the primary functions of the prefrontal cortex?

See page 89 for the answer.

Beyond Gray Matter: The Connections

Historically, most researchers have concentrated more on the cell bodies (gray matter) than on the connections among them (white matter). However, behavior and experience depend on the communication among cells, and that depends on the connections. The **Human Connectome Project** is an effort to map all the long-distance connections, analogous to the way the human genome project mapped all the genes on the chromosomes. Researchers have already demonstrated many correlations between brain connections and behavioral tendencies, and they expect to find abnormal connections responsible for many psychological disorders (Szalkai et al., 2019; Tozzi et al., 2020).

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How Do the Parts Work Together?

If you shake a jar of popcorn, you perceive that what you see is also what you feel and what you hear. How do you do that? Vision, touch, and hearing activate cortical areas that have only weak connections with one another. Even in vision, the area that responds to shape is separate from the area responsible for seeing the object's color, the area detecting its movement, and the area detecting its location in space. Nevertheless, you perceive a colored object at a particular place and moving a certain way. Karl Lashley (1949) noticed this problem long ago, but neuroscientists did not pay much attention to it until the 1990s.[1]

The question of how various brain areas produce a perception of a single object is known as the **binding problem**, or *large-scale integration* problem. In an earlier era, researchers assumed that various kinds of sensory information converge in areas that associate one sensation with another. However, all information does not feed into a central "little person in the head." Relatively few cells combine one sense with another (Blanke, 2012). Even when they do, they don't explain how we bind sensory information. For example, certain neurons in the posterior temporal cortex respond both when you see a chain saw and when you hear the sound it makes (Man et al., 2012). But surely you weren't born knowing what sound a chain saw makes. Somehow those cells developed their properties through experience.

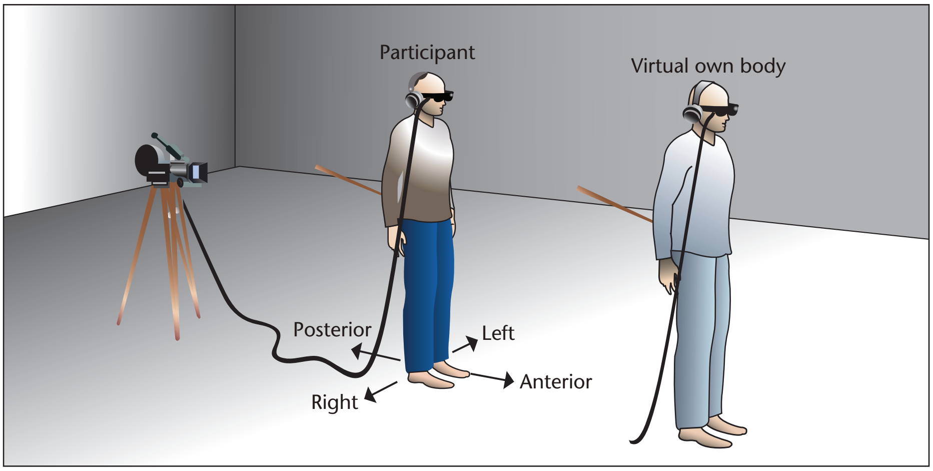
Although no one can fully explain binding, we know what is necessary for it to occur: It occurs if you perceive two sensations as happening at the same time at approximately the same place. When a skilled ventriloquist says something and makes the dummy's mouth move at the same time, you perceive the sound as coming from the dummy. As part of this illusion, the visual stimulus alters the response of the auditory cortex, so that the sound really does seem to come from the same location as the dummy's mouth (Bonath et al., 2007; Bruns et al., 2011). In contrast, if you watch a poorly dubbed foreign-language film, the lips do not move at the same time as the speech, and you perceive that the words did *not* come from those lips.

Applying these principles, researchers arranged a camera to video someone's back, and they simultaneously sent the pictures to a three-dimensional display mounted to the person's head, as in Figure 3.25. Imagine that you are the participant. As you view the video of your back, it appears to be 2 meters in front of you. Then someone strokes your back. You simultaneously feel the touch and see the action that appears to be 2 meters in front. After a while, you start perceiving your body as being 2 meters in front of you! When told to "please return to your seat," you walk to a spot displaced from the actual seat, as if you were actually 2 meters forward from your current position (Lenggenhager et al., 2007).

Suppose you see a light flash once while you hear two beeps. You will sometimes think you saw the light flash twice. If the tone is soft, you may experience the opposite: The tone beeps twice during one flash of light,

Figure 3.25 Where Am I?

As someone stroked the person's back, a video camera relayed the information so the person could view it, appearing to be a few feet ahead. After a few minutes, the person felt as if the body were in fact a few feet ahead of where it was.



From "Video ergo sum: Manipulating bodily self-consciousness," by B. Lenggenhager, T. Tadi, T. Metzinger, and O. Blanke, 2007, *Science, 317*, pp. 1096–1099.

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[1] The third verse of the Christian hymn "For the Beauty of the Earth" includes the phrase "For the mystic harmony linking sense to sound and sight." Evidently the author of this hymn noticed the theoretical issue more than a hundred years earlier.

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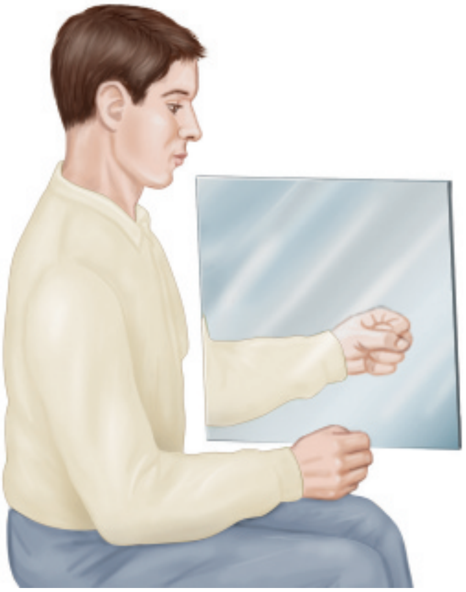
and you think you heard only one beep. If you saw three flashes of light, you might think you heard three beeps (Andersen et al., 2004). The near simultaneity of lights and sounds causes you to bind them and perceive an illusion that alters your perception of one or the other. Binding might fail if the displays are flashed very briefly or while you are distracted (Holcombe and Cavanagh, 2001; Lehky, 2000).

Here is another great demonstration (Robertson, 2005). Position yourself parallel to a large mirror, as in Figure 3.26, so that you see your right hand and its reflection in the mirror. Keep your left hand out of sight. Now repeatedly clench and unclench both hands in unison. Wiggle your fingers, touch your thumb to each finger, and so forth, in each case doing the same thing with both hands at the same time. You will continually feel your left hand doing the same thing you see the hand in the mirror doing, which (being the mirror image of your right hand) looks like your left hand. After 2 or 3 minutes, you may start to feel that the hand in the mirror is your own left hand.

In a variant of this procedure, researchers arranged to touch someone's real right hand and a rubber hand next to it, both at the same time and in the same way, allowing the person to see both hands. Within minutes, people reported feeling that they had two right hands, in addition to the unseen left hand (Guterstam et al., 2011). That experience fades if the stimulation stops, or if the stimulation differs between the real hand and the rubber hand (Pfister et al., 2021). So, the evidence indicates that we bind two experiences that occur at the same time. Still, the theoretical question remains of exactly how we do so.

Figure 3.26 An illusion to demonstrate binding

Clench and unclench both hands while looking at your right hand and its reflection in the mirror. Keep your left hand out of sight. After a couple of minutes, you may start to experience the hand in the mirror as being your own left hand.



Stop & Check

16. What is meant by the binding problem, and what is necessary for binding to occur?

See page 89 for the answer.

Module 3.2 | In Closing

Functions of the Cerebral Cortex

The cerebral cortex is the largest portion of the human brain, but it is not the entire brain. Its primary function seems to be one of elaborating sensory information and organizing sequences of behaviors. Even fish, which have no cerebral cortex, can see and hear, but the cerebral cortex enables us to add great complexity.

Summary

1. Although brain size varies among mammalian species, the overall organization is similar. **81**
2. The cerebral cortex has six laminae (layers) of neurons. The cortex is also organized into columns of cells arranged perpendicular to the laminae. **82**
3. The occipital lobe of the cortex is primarily responsible for vision. Damage to part of the occipital lobe leads to blindness in part of the visual field. **83**
4. The parietal lobe processes body sensations. The postcentral gyrus contains four representations of the body. **83**
5. The temporal lobe contributes to hearing, complex aspects of vision, and processing of emotional information. **84**

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6. The frontal lobe includes the precentral gyrus, which controls fine movements. It also includes the prefrontal cortex. **85**
7. The prefrontal cortex is important for planning actions, aspects of memory and cognition, and decision making. **86**
8. The binding problem is the question of how we connect activities in different brain areas, such as sights and sounds. Binding requires perceiving that two types of stimuli (such as sight and sound) occurred at the same place at the same time. **87**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary, at the end of this book.

anterior commissure **81**
binding problem **87**
central sulcus **83**
cerebral cortex **81**
columns **82**
corpus callosum **81**
default network **85**
frontal lobe **85**
Human Connectome Project **86**
Klüver-Bucy syndrome **84**
laminae **82**
occipital lobe **83**
parietal lobe **83**
postcentral gyrus **83**
precentral gyrus **85**
prefrontal cortex **85**
prefrontal lobotomy **86**
primates **81**
temporal lobe **84**
temporoparietal junction **84**

Thought Question

When monkeys with Klüver-Bucy syndrome pick up lighted matches and snakes, we do not know whether they are displaying an emotional deficit or an inability to identify the object. What kind of research method might help answer this question?

Stop & Check Answers

10. Lamina IV, which receives sensory input, is thickest in areas that deal with sensation. Lamina V, with motor output, is thickest in areas that control movement.
11. Temporal lobe
12. Parietal lobe
13. Occipital lobe
14. Frontal lobe
15. The posterior portion contributes to control of movement. The middle portion pertains to working memory, cognitive control, and emotion. The anterior portion compares various types of information for making a decision.
16. The binding problem is the question of how the brain combines activity in different brain areas to produce unified perception. Binding requires identifying the location of an object and perceiving all aspects of a stimulus as being simultaneous. When the sight and sound appear to come from the same location at the same time, we bind them as a single experience.

Module 3.2 | End-of-Module Quiz

1. Which area occupies about the same percentage of the brain in almost all mammals?
   - **a.** The cerebral cortex
   - **b.** The prefrontal cortex
   - **c.** The cerebellum
   - **d.** The primary visual cortex

2. The cerebral cortex has (at most) how many laminae?
   - **a.** Two
   - **b.** Three
   - **c.** Five
   - **d.** Six

3. If a group of neurons have similar properties, what is probably true of them?
   - **a.** They have the same number of dendrites.
   - **b.** One is in the left hemisphere and the other is in the right hemisphere.
   - **c.** They are in the same lamina.
   - **d.** They are in the same column.

4. The occipital cortex includes the primary area for what sense?
   - **a.** Hearing
   - **b.** Vision
   - **c.** Smell
   - **d.** Touch

5. Where is the primary somatosensory cortex?
   - **a.** Precentral gyrus
   - **b.** Postcentral gyrus
   - **c.** Temporoparietal junction
   - **d.** Cingulate cortex

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6. Which human cortical area is specialized for hearing, language, and face recognition?
- **a.** Temporal lobe
- **b.** Frontal lobe
- **c.** Parietal lobe
- **d.** Occipital lobe

7. Where is the primary motor cortex?
- **a.** Precentral gyrus
- **b.** Postcentral gyrus
- **c.** Temporoparietal junction
- **d.** Cingulate cortex

8. Which cortical area is specialized for choosing the action with the best probable outcome?
- **a.** Fusiform gyrus
- **b.** Anterior prefrontal cortex
- **c.** Occipital cortex
- **d.** Postcentral gyrus

9. What is the binding problem?
- **a.** The difficulty of coordinating the left side of the body with the right side
- **b.** The difficulty of synchronizing output from a population of axons
- **c.** The question of how we perceive separate sensations as a single object
- **d.** The question of how a bilingual person shifts from one language to another

10. When are we likely to bind visual, auditory, and touch stimuli?
- **a.** If they produce action potentials of similar amplitude
- **b.** If they are equally familiar
- **c.** If they appear to come from the same place at the same time
- **d.** If they send their initial signals to the same nucleus of the thalamus

---

Answers: 1c, 2d, 3d, 4b, 5b, 6a, 7a, 8b, 9c, 10c.

Module 3.3

Research Methods

Learning Objectives

After studying this module, you should be able to:

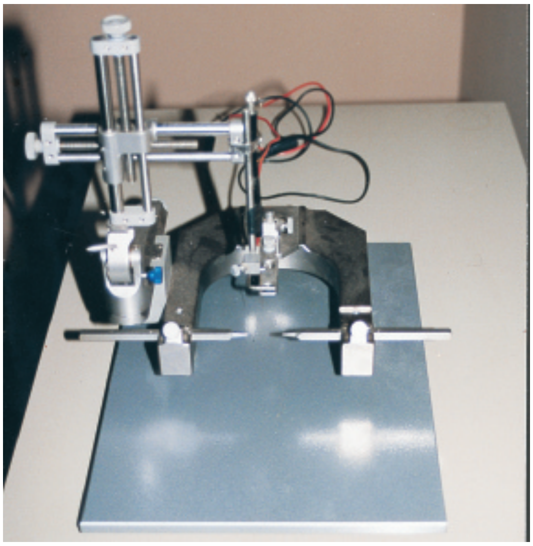
8. Describe major methods for studying the relationship between brain activity and behavior.
9. Note the strengths and limitations of each method.

In this text, we consider many methods of relating the brain's structure to its function. This module overviews four categories and the logic behind them:

1. *The effects of brain damage.* After damage or inactivation of a brain area, how does behavior change?
2. *The effects of stimulating a brain area.* What happens after stimulation of some brain area?
3. *Brain activity during behavior.* Which brain areas increase or decrease their activity during some type of behavior?
4. *Correlations of brain anatomy with behavior.* Do people or animals with some unusual behavior also have unusual brains? If so, in what way?

Figure 3.27 A stereotaxic instrument for locating brain areas in small animals

Using this device, researchers can insert an electrode to stimulate, record from, or damage any point in the brain.



James Kalat

Effects of Brain Damage

In 1861, the French neurologist Paul Broca found that a patient who had lost the ability to speak had damage in part of his left frontal cortex. Additional patients with speech impairments also exhibited damage in and around that area, now known as *Broca's area*. This discovery revolutionized neurology, because it demonstrated for the first time that different brain areas have different functions.

Since then, researchers have made countless reports of behavioral impairments after brain damage. Brain damage can impair the ability to recognize faces, to perceive motion, or to pay attention to the left side of the world. It can alter motivation, emotion, memory, or social behavior. The implications are deep: If you lose part of your brain, you lose part of your mind.

Although many interesting results come from people with brain damage, human studies have limitations. Few people have damage confined to just one brain area, and each person's pattern of brain damage is unique. Therefore researchers often turn to producing carefully localized damage in laboratory animals. An **ablation** is the removal of a brain area, generally with a surgical knife. Because surgical removal is difficult for tiny structures below the surface of the brain, researchers sometimes make a **lesion**, meaning damage, by means of a **stereotaxic instrument**, a device for the precise placement of electrodes in the brain (Figure 3.27). By consulting a stereotaxic atlas (map) of a species' brain, a researcher aims an electrode at the desired position relative to landmarks on the skull. The researcher anesthetizes an animal, drills a small hole in the skull, inserts the electrode (insulated except at the tip), lowers it to the target, and passes an electrical current to damage that area. For comparison, the experimenter produces a *sham lesion* in a control group, performing all the same procedures except for passing the electrical current. Any behavioral difference between the two groups must result from the lesion and not the other procedures. Stereotaxic surgery used to be a common procedure, but it declined as other methods became available. A stereotaxic device can also be used to implant an electrode to record from cells.

Another method is injecting a chemical that kills neurons or inactivates them temporarily, without harming the passing axons. Researchers can also inject a chemical that disables a particular type of synapse. Still another option is the *gene-knockout approach* that directs a mutation to a gene that regulates one type of cell, transmitter, or receptor.

Transcranial magnetic stimulation (TMS), the application of magnetic stimulation to a portion of the scalp, stimulates neurons below the magnet if the stimulation is brief and mild, but with stronger stimulation it inactivates the neurons, producing a "virtual lesion" that outlasts the magnetic stimulation itself (Dayan et al., 2013). This procedure enables researchers to study behavior with a brain area active, then inactive, and then active again. Figure 3.28 illustrates the apparatus. One study found that after TMS silenced the hand area of the motor cortex, people had trouble mentally rotating the hand in a picture to imagine how it would appear from a different angle (Ganis et al., 2000). That is, when you imagine seeing your hand from a different angle, you imagine *moving* it, not just seeing it move.

After any kind of brain damage or inactivation, the problem for psychologists is to specify the exact behavioral deficit. If damaging a brain area makes an animal stop eating, you don't know why. Did it lose its hunger? Its ability to taste food? Its ability to find the food? Its ability to move at all? You need further behavioral tests to explore the possibilities.

Stop & Check

17. What is the difference between a lesion and an ablation?

See page 99 for the answer.

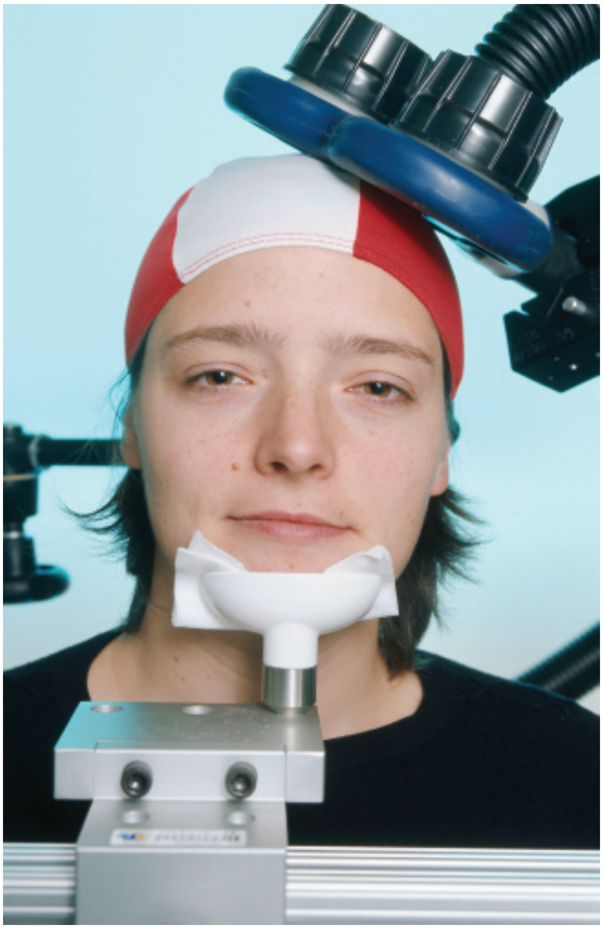
Effects of Brain Stimulation

If brain damage impairs a behavior, stimulation should increase it. The old-fashioned way is to insert an electrode into an animal's brain and deliver brief, mild currents to an area. That method has limited value, because the electrical current stimulates many types of neurons in an area, as well as the axons passing through.

A popular approach today is **optogenetics**, using light to control a limited population of neurons. Development of this method required three steps, each of which would be useless without the others, and each of which seemed almost impossible. Despite the enormous reasons for pessimism, Karl Deisseroth and his colleagues persisted in efforts for years, until the method was ready for wide use in 2009 (Deisseroth, 2015).

Figure 3.28 Apparatus for magnetic stimulation of a human brain

The procedure is known as transcranial magnetic stimulation, or TMS.


BSIP SA/Alamy Stock Photo

(**Source:** Marina Chicurel)

The first step was to discover or invent a protein that responds to light by producing an electrical current. Certain microbes produce such proteins, which researchers found ways to modify. One protein reacts to light by opening a sodium channel, exciting the neuron, and another reacts by opening a chloride channel, producing inhibition. The second step was to develop viruses that insert one of these proteins into a certain type of neuron, or even to just one part

C Flanigan/FilmMagic/ Getty Images

Karl Deisseroth

[A] final point [is] the essential value of exploratory basic science research. . . . It seems unlikely that the initial experiments described here would have been fundable, as such, by typical grant programs focusing on a disease state. . . . [T]he advances brought by microbial opsin-based optogenetics may inform the pathophysiology of neurological and psychiatric disease states . . . in addition to the broad basic science discoveries." (Deisseroth, 2015, p. 1224)

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of the neuron, such as the axon or the dendrites (Packer et al., 2013). The third step was to develop very thin optical fibers that can shine just the right amount of light onto neurons in a narrowly targeted area. Using these methods, an investigator can excite or inhibit a single type of neuron in a small brain area with millisecond accuracy, determining the function of cells in greater detail than ever before. Because of the invasive nature of the method, it could be used in humans only when it might produce a medical benefit.

Stop & Check

18. What determines whether optogenetic stimulation excites a neuron or inhibits it?

See page 99 for the answer.

Recording Brain Activity

During any behavior or experience, activity increases in some brain areas and decreases in others. Mapping those areas helps to identify their functions.

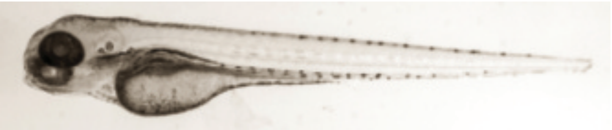
Some studies use animals with specialized features. Here is an example: Zebrafish larvae are small and almost transparent. Even their brains are transparent (Figure 3.29). Researchers modify the fish genetically so that proteins in the brain fluoresce when a neuron is active. Then they monitor the neurons, watching which ones become active during any behavior. This method demonstrated that one set of neurons responds while the fish hunts for food, another set responds while the fish swims to explore a new area, and yet another set controls transitions between hunting and exploring (Marques et al., 2020).

To record brain activity in mammals, researchers use other methods. For many years, researchers relied on inserting an electrode to record activity from one neuron. New technologies enable researchers to use tiny electrodes that record from hundreds of neurons at once, without significantly interrupting normal function (Paulk et al., 2022; Vázquez-Guardado et al., 2020).

Occasionally, researchers insert electrodes to record activity while a human brain is exposed preliminary to brain surgery. This method can be highly valuable scientifically, but it does raise ethical questions, especially about whether the patient gave informed consent without a sense of obligation (Feinsinger et al., 2022).

Figure 3.29 A zebrafish larva

Because it is small and transparent, researchers can observe the activity of all its neurons while it is behaving naturally.



Micha Weber/Shutterstock.com

More often, human research relies on noninvasive methods—that is, recordings from outside the skull. An **electroencephalograph (EEG)** records electrical activity of the brain through electrodes, ranging from just a few to more than a hundred, attached to the scalp (Figure 3.30). Electrodes glued to the scalp measure the average activity at any moment for the population of cells under the electrode. An EEG is useful for distinguishing between wakefulness and various stages of sleep. It can also help with the diagnosis of epilepsy, although a physician may need to conduct the test repeatedly or test the person under special conditions (Renzel et al., 2016; Salinsky et al., 1987). The same device used for an EEG can also record brain activity in response to a stimulus, in which case we call the results **evoked potentials** or **evoked responses**.

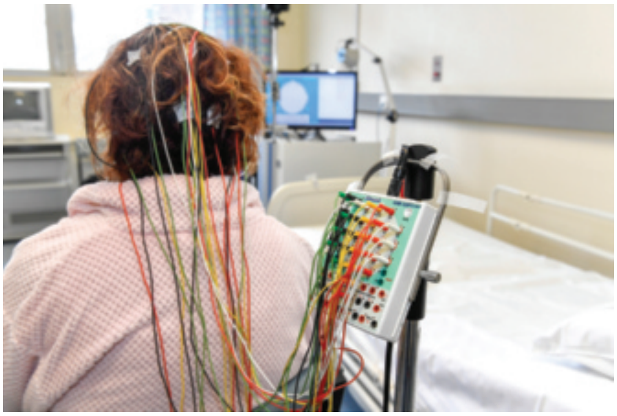
A **magnetoencephalograph (MEG)** is similar, but instead of measuring electrical activity, it measures the faint magnetic responses generated by brain activity (Hari, 1994). An MEG has excellent temporal resolution, able to record changes from one millisecond to the next.

Figure 3.31 shows an MEG record of brain responses to a brief tone heard in the right ear. The diagram represents a human head as depicted from above, with the nose at the top (Hari, 1994). Researchers using an MEG can identify the times when various brain areas respond and thereby trace a wave of brain activity from its origin to the other areas that process it (Salmelin et al., 1994).

Positron-emission tomography (PET) provides a high-resolution image of activity in a living brain. First, the person receives an injection of glucose labeled with radioactive atoms. Because the most active brain areas increase their intake of glucose, tracking the glucose identifies areas of increased activity. When a radioactive atom decays, it releases a positron that collides with a nearby electron, emitting two gamma rays in opposite directions. The person's head is surrounded by a set of

Figure 3.30 Electroencephalography

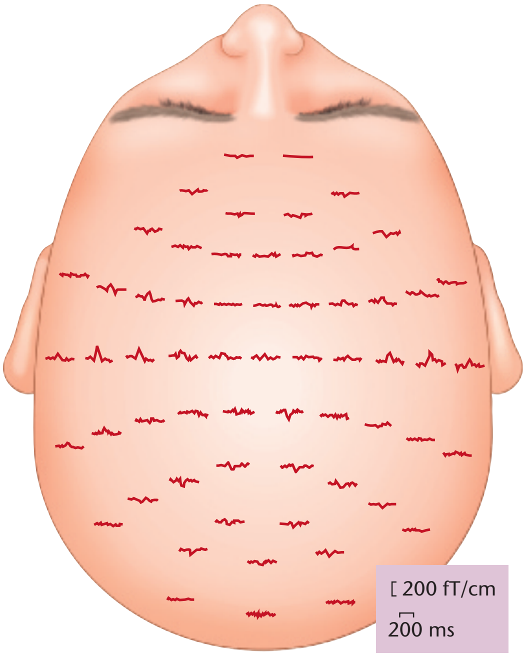
An electroencephalograph records the overall activity of neurons under various electrodes attached to the scalp.



DR P. MARAZZI/Science Source

Figure 3.31 A result of magnetoencephalography, illustrating responses to a tone in the right ear

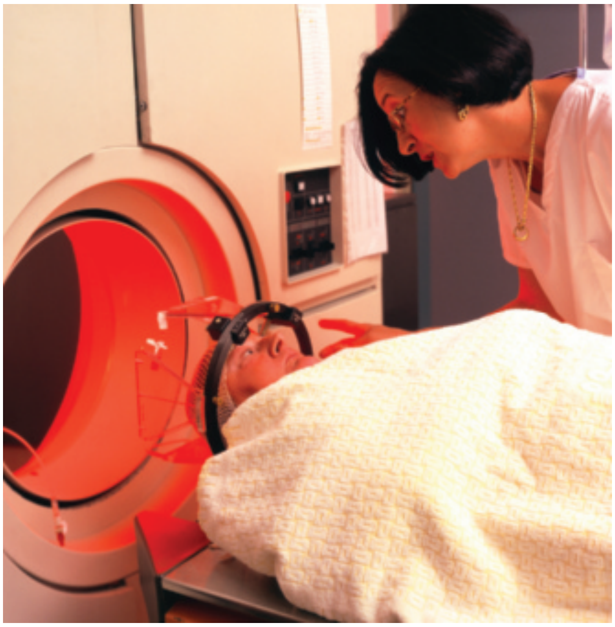
The nose is displayed at the top. For each spot on the diagram, the display shows the changing response over a few hundred milliseconds following the tone. (Note calibration at lower right.) The tone evoked responses in many areas, with the largest responses in the temporal cortex, especially on the left side.



(**Source:** Reprinted from *Neuroscience: From the Molecular to the Cognitive,* by R. Hari, 1994, p. 165, with kind permission from Elsevier Science—NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.)

Figure 3.32 A PET scanner

A person engages in a cognitive task while attached to this apparatus; the PET scanner records which areas of the brain become more active and by how much.



CC STUDIO/Science Source

gamma ray detectors (Figure 3.32). When two detectors record gamma rays at the same time, a computer identifies a spot halfway between them as the origin of the gamma rays. The computer uses this information to determine which areas have the most glucose, which are therefore the areas with greatest activity (Phelps and Mazziotta, 1985).

PET scans use radioactive chemicals with a short half-life, made in a device called a cyclotron. Because cyclotrons are expensive, PET is available only at research hospitals. Furthermore, PET requires exposing the brain to radioactivity, not much, but nevertheless a potential hazard, especially if repeated. For most purposes, researchers have replaced PET scans with **functional magnetic resonance imaging (fMRI)**, which is less expensive and less risky. Standard MRI scans record the energy released by water molecules after removal of a magnetic field. An fMRI is a modified version based on hemoglobin (the blood protein that binds oxygen) instead of water. Hemoglobin bound to oxygen reacts to a magnetic field differently from hemoglobin without oxygen. When a brain area becomes more active, it uses more oxygen and the percentage of hemoglobin bound to oxygen decreases. An fMRI scanner detects that change (Sirotin et al., 2009; Viswanathan and Freeman, 2007). Figure 3.33 depicts an example.

Each method has advantages and disadvantages. EEG and MEG provide precise information about the timing

Figure 3.33 An fMRI scan of a human brain

An fMRI produces an image with a spatial resolution of 1 to 2 mm and temporal resolution of about a second.

patrickheagney/Getty Images

(**Source:** Wagner et al., 1998)

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of activity, but only approximate information about location, and they are sensitive only to cells near the surface of the brain. PET and fMRI provide more detailed information about the location of activity, but only approximate information about its timing. PET and fMRI also have the disadvantage that they require so much time and effort that researchers almost never assemble data on a large sample of people.

An fMRI while you were, for example, reading would mean nothing without a comparison to something else. Researchers would record your brain activity while you were reading and during a comparison task, and then compare the brain activity for the two tasks. As a comparison task, researchers might ask you to read a page written in a language you do not understand. Figure 3.34 illustrates the idea.

Interpreting the meaning of fMRI data can be difficult. Consider the result that certain types of reward activate the dorsal striatum, which is part of the basal ganglia. If the dorsal striatum later becomes active while people are doing something, does that activity mean that people find the activity rewarding? Not necessarily, unless we know that the dorsal striatum is active *only* during reward (Poldrack, 2006).

The data from fMRI sometimes provide valuable psychological information. Here are two examples:

1. Many people in pain report decreased pain after they receive a placebo (a drug with no pharmacological activity). Do they really feel less pain, or are they just saying so? Studies with fMRI demonstrate that brain areas responsible for pain really do decrease their response (Wager and Atlas, 2013).
2. Psychologists distinguish several types of memory, such as implicit versus explicit, and declarative versus procedural. One perspective is that every memory task is one or the other. If so, different types of memory should activate different sets of brain areas. An alternative opinion is that memory has several components that are active to different degrees in different situations. The fMRI data fit that view better: Most memory tasks activate the same brain areas, but to varying degrees (Cabeza and Moscovitch, 2013).

Studies using fMRI data depend on averages over many trials, and usually over a group of individuals. The results provide good evidence for general trends, but in most cases, they are not reliable enough to draw conclusions about an individual person (Elliott et al., 2020; Kragel et al., 2021).

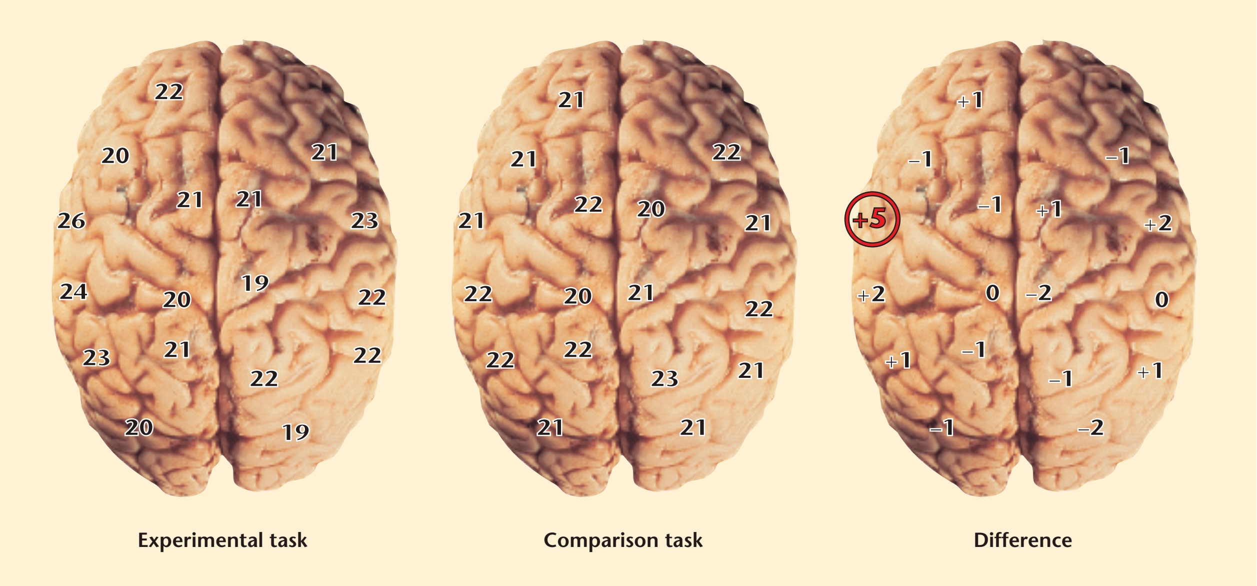
Stop & Check

19. What does fMRI measure?
20. Suppose fMRI research demonstrates that a particular brain area becomes active when people listen to music. When that area becomes active later, can we conclude that a person is listening to or thinking about music?

See page 99 for the answer.

Figure 3.34 Subtraction for a brain scan procedure

Numbers on the brain at the left illustrate hypothetical levels of arousal during some task, measured in arbitrary units. The brain at the center depicts activity in the same brain areas during a comparison task. The brain at the right indicates the differences. The highlighted area has the largest difference. In actual data, the largest increases in activity would be one-tenth or two-tenths of a percent.



Dr. Dana Copeland

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Correlating Brain Anatomy with Behavior

One of the first ways ever used for studying brain function sounds easy: Find someone with unusual behavior and then look for unusual features of the brain. In the 1800s, Franz Gall observed some people with excellent verbal memories who had protruding eyes. He inferred that verbal memory depended on brain areas behind the eyes that had pushed the eyes forward. Gall then examined the skulls of people with other talents or personalities. He assumed that bulges and depressions on their skull corresponded to the brain areas below them. His process of relating skull anatomy to behavior is known as **phrenology**. One of his followers made the phrenological map in Figure 3.35.

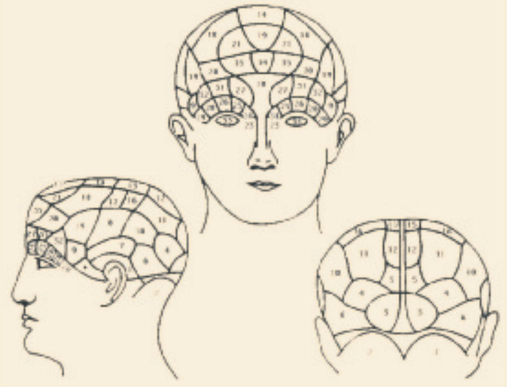
Phrenology was a pseudoscience, but the idea behind it wasn't altogether wrong. If people with a particular psychological strength or weakness share some unusual feature of the brain, then we can draw inferences about that brain area. Phrenologists' problems were, first, that the bumps on the skull don't correlate reliably with the anatomy of the brain beneath them, and second, that the phrenologists drew conclusions based on small numbers of people and analyzed their behavior only superficially.

Today, researchers can examine detailed brain anatomy in living people. One method is **computerized axial tomography**, better known as a **CT** or **CAT scan** (Andreasen, 1988). A physician injects a dye into the blood to increase contrast in the image, and then places the person's head into a scanner like the one illustrated in Figure 3.36a. X-rays pass through the head to be recorded by detectors on the opposite side. The scanner rotates slowly to take a measurement at each angle. From the measurements, a computer constructs images of the brain. Figure 3.36b is an example. CT scans help detect tumors and other structural abnormalities.

Another method is **magnetic resonance imaging (MRI)** (Warach, 1995), based on the fact that any atom with an odd-numbered atomic weight, such as hydrogen, has an axis of rotation. An MRI device applies a powerful magnetic field (about 25,000 times the magnetic field of the Earth) to align all the axes of rotation, and then tilts them

Figure 3.35 A phrenologist's map of the brain

Neuroscientists today also try to localize functions in the brain, but they use more careful methods and they study such functions as vision and hearing, not "secretiveness" and "marvelousness."



Affective Faculties

Propensities
? Desire to live
• Alimentiveness
1 Destructiveness
2 Amativeness
3 Philoprogenitiveness
4 Adhesiveness
5 Inhabitiveness
6 Combativeness
7 Secretiveness
8 Acquisitiveness
9 Constructiveness

Sentiments
10 Cautiousness
11 Approbativeness
12 Self-esteem
13 Benevolence
14 Reverence
15 Firmness
16 Conscientiousness
17 Hope
18 Marvelousness
19 Ideality
20 Mirthfulness
21 Imitation

Intellectual Faculties

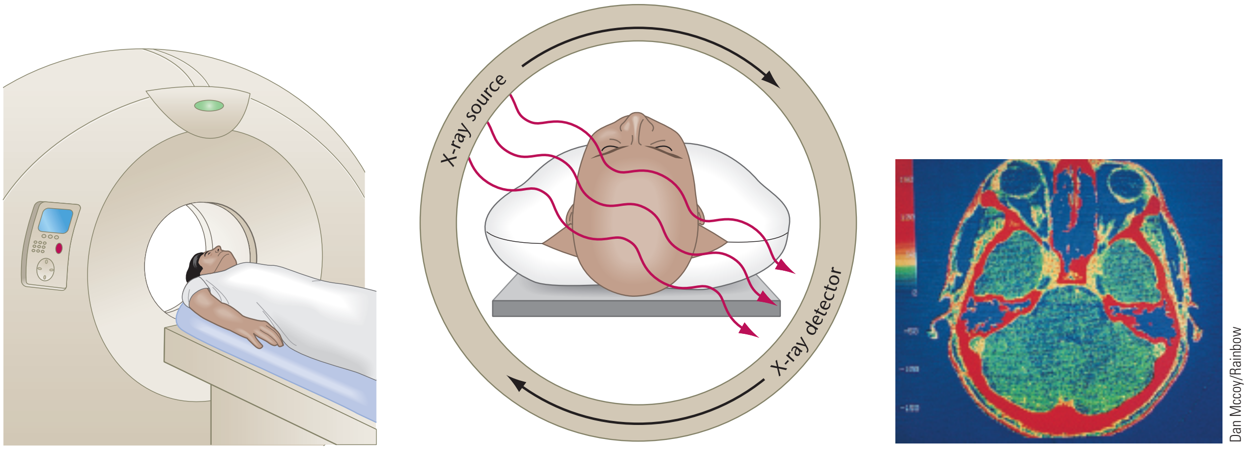
Perceptive
22 Individuality
23 Configuration
24 Size
25 Weight and resistance
26 Coloring
27 Locality
28 Order
29 Calculation
30 Eventuality
31 Time
32 Tune
33 Language

Reflective
34 Comparison
35 Causality

(**Source:** From Spurzheim, 1908)

Figure 3.36 CT scanner

(a) A person's head is placed into the device and then a rotating source sends X-rays through the head while detectors on the opposite side make photographs. A computer constructs an image of the brain. (b) An image of a normal human brain generated by computerized axial tomography (CT scanning).



(a)

(b)

(**Source:** Dan McCoy/Rainbow)

with a brief radio frequency field. When the radio frequency field is turned off, the atomic nuclei release electromagnetic energy as they relax and return to their original axis. By measuring that energy, MRI devices form an image of the brain, such as the one in Figure 3.37. MRI can depict anatomical details smaller than a millimeter in diameter. One drawback is that the person must lie motionless in a confining, noisy apparatus. The procedure is usually not suitable for children or anyone who fears enclosed places, but clever experimenters have found ways to modify the procedure for children, infants, and even mice.

Researchers using these methods can relate behaviors to the sizes of brain areas. Doing so can be fruitful when we are trying to understand an unusual condition, such as people who are unable to recognize faces (Lohse et al., 2016) or people who quickly learn dozens of languages (Amunts et al., 2004). However, to study the brain differences associated with normal behaviors, researchers would generally need large samples, probably a thousand or more, to get reliable results (Marek et al., 2022). For example, researchers reported correlations between the size of the amygdala and people's political orientation or their number of Facebook friends, based on small samples. Other researchers failed to replicate those findings (Genon et al., 2022). Table 3.5 summarizes various methods of studying brain-behavior relationships.

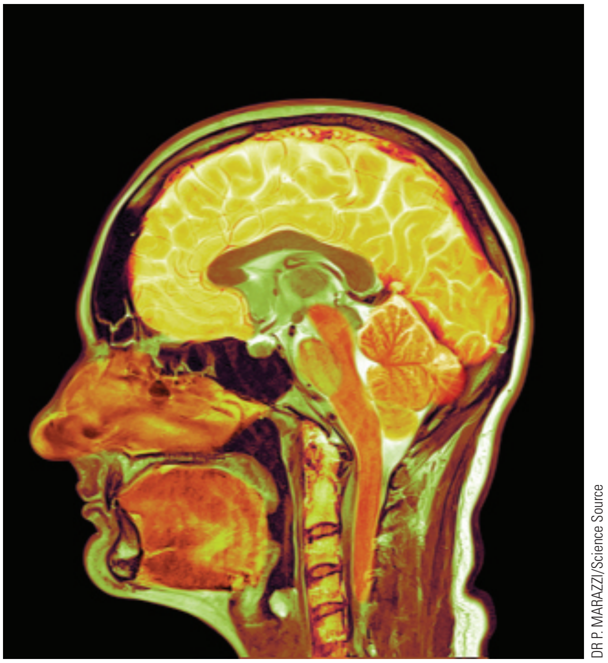
Stop & Check

21. What are the similarities and differences between MRI and fMRI?

See page 99 for the answer.

Figure 3.37 A view of a living brain generated by magnetic resonance imaging

Any atom with an odd-numbered atomic weight, such as hydrogen, has an inherent rotation. An outside magnetic field can align the axes of rotation. A radio frequency field can then make the atoms move like tiny gyros. When the radio frequency field is turned off, the atomic nuclei release electromagnetic energy as they relax. By measuring that energy, we can obtain an image of a structure such as the brain.



(**Source:** Dan McCoy/Rainbow)

Table 3.5 | Methods of Studying Brain-Behavior Relationships

Examine Effects of Brain Damage	
Study victims of stroke, etc.	Used with humans; each person has different damage
Lesion	Controlled damage in laboratory animals
Ablation	Removal of a brain area
Gene knockout	Affects wherever that gene is active (e.g., a receptor)
Transcranial magnetic stimulation	Intense application temporarily inactivates a brain area
Examine Effects of Stimulating a Brain Area	
Stimulating electrodes	Invasive; used with laboratory animals, rarely with humans
Optogenetic stimulation	Almost always with laboratory animals; can indicate function of a particular type of cell
Record Brain Activity during Behavior	
Record from electrodes in brain	Invasive; used with laboratory animals, rarely with humans
Electroencephalograph (EEG)	Records from scalp; measures changes by milliseconds, but with low resolution of location of the signal
Evoked potentials	Similar to EEG but in response to stimuli
Magnetoencephalograph (MEG)	Similar to EEG but measures magnetic fields
Positron emission tomography (PET)	Measures changes over both time and location but requires exposing brain to radiation
Functional magnetic resonance imaging (fMRI)	Measures changes over about 1 second, identifies location within 1 to 2 mm
Correlate Brain Anatomy with Behavior	
Computerized axial tomography (CAT)	Maps brain areas, using X-rays
Magnetic resonance imaging (MRI)	Maps brain areas in detail, using magnetic fields

Module 3.3 | In Closing

Research Methods and Progress

In any scientific field—indeed, any field of knowledge—progress almost always depends on improved measurement. In astronomy, improvements in both ground-based and satellite-based astronomy have established conclusions that even science-fiction writers couldn't have imagined. Weather prediction is vastly more accurate than it used to be. Similarly, our understanding of the brain has advanced greatly because of the introduction of PET scans, fMRI, optogenetics, and other modern technologies. Future progress will continue to depend on further improvements in measurement.

Summary

1. One way to study brain-behavior relationships is to examine the effects of brain damage. If someone suffers a loss after some kind of brain damage, then the damaged area contributes in some way to that behavior. **91**
2. If stimulation of a brain area increases a behavior, presumably that area contributes to the behavior. Optogenetics is a relatively new method that enables researchers to stimulate a particular type of cell at a particular moment. **92**
3. Researchers try to understand brain-behavior relationships by recording activity in brain areas during a given behavior. Methods include EEG, MEG, PET, and fMRI. **93**
4. People who differ with regard to some behavior sometimes also differ with regard to brain anatomy. MRI is a modern method of imaging a living brain. However, correlations between behavior and anatomy should be evaluated cautiously. **96**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary, at the end of this book.

ablation **91**
computerized axial tomography (CT or CAT scan) **96**
electroencephalograph (EEG) **93**
evoked potentials or evoked responses **93**
functional magnetic resonance imaging (fMRI) **94**
lesion **91**
magnetic resonance imaging (MRI) **96**
magnetoencephalograph (MEG) **93**
optogenetics **92**
phrenology **96**
positron-emission tomography (PET) **93**
stereotaxic instrument **91**
transcranial magnetic stimulation (TMS) **92**

Thought Question

Certain unusual aspects of brain structure were observed in the brain of Albert Einstein (Falk et al., 2013). One interpretation is that he was born with certain specialized brain features that encouraged his scientific and intellectual abilities. What is an alternative interpretation?

Stop & Check Answers

17. A lesion is damage to a structure. An ablation is removal of the structure.

18. Optogenetic stimulation activates a light-sensitive protein. If that protein opens a sodium channel in the membrane, the result is excitation of the neuron. If it opens a chloride channel, the result is inhibition.

19. It detects the percentage of hemoglobin lacking oxygen.

20. No, because the area may perform functions in addition to music. Also, fMRI data are not reliable enough to draw any conclusions about an individual.

21. Both methods measure the responses of brain chemicals to a magnetic field. MRI depicts the anatomy of the brain. The fMRI method shows which brain areas are most active at the moment.

Module 3.3 | End-of-Module Quiz

1. The first demonstration that a brain area controlled a particular aspect of behavior pertained to which type of behavior?

- **a.** Criminal activity
- **b.** Language
- **c.** Hunger
- **d.** Sexual arousal

2. Why is it difficult to draw scientific conclusions from the study of human brain damage?

- **a.** Brain-damaged people cannot understand the instructions.
- **b.** It is illegal to seek informed consent from brain-damaged people.
- **c.** Most people recover quickly after brain damage.
- **d.** Few people have damage to one and only one area.

3. What method can produce a temporary "virtual lesion" of a brain area?

- **a.** Stereotaxic instrument
- **b.** Optogenetics
- **c.** Transcranial magnetic stimulation
- **d.** Positron-emission tomography

4. What method can control excitation or inhibition of a particular type of cell in a single area with millisecond accuracy?

- **a.** Stereotaxic instrument
- **b.** Optogenetics
- **c.** Transcranial magnetic stimulation
- **d.** Positron-emission tomography

5. Why are zebrafish larvae useful for certain types of brain research?

- **a.** They are transparent.
- **b.** They are immobile.
- **c.** All their neurons use the same neurotransmitter.
- **d.** Their neurons are large and similar from one individual to another.

6. Which methods are most useful for detecting momentary changes in brain activity?

- **a.** Stereotaxic instruments and CRISP-R
- **b.** Optogenetics and transcranial magnetic stimulation
- **c.** EEG and MEG
- **d.** PET and fMRI

7. Which methods are most useful for detecting the location of brain areas that become active during some behavior?
   - **a.** Stereotaxic instruments and CRISP-R
   - **b.** Optogenetics and transcranial magnetic stimulation
   - **c.** EEG and MEG
   - **d.** PET and fMRI

8. Which of these is the first step for positron-emission tomography (PET)?
   - **a.** Inject a radioactive chemical into the blood.
   - **b.** Insert an electrode into the brain.
   - **c.** Subject the brain to a strong magnetic field.
   - **d.** Attach light-sensitive proteins to a virus.

9. What is one advantage of fMRI over PET scans?
   - **a.** The fMRI technique measures activity on a millisecond-by-millisecond basis.
   - **b.** The fMRI technique does not require inserting an electrode into the head.
   - **c.** The fMRI technique does not expose the brain to radioactivity.
   - **d.** The fMRI technique identifies which brain areas are most active at a given moment.

10. Why should no one draw conclusions about a given individual based on fMRI results?
    - **a.** The fMRI method is still considered "experimental."
    - **b.** The fMRI method measures only the surface of the cortex.
    - **c.** The fMRI results take too long to analyze.
    - **d.** The fMRI results do not have high enough reliability.

Answers: 1b, 2d, 3c, 4b, 5a, 6c, 7d, 8a, 9c, 10d.

Suggestions for Further Reading

Burrell, B. (2004). *Postcards from the brain museum.* New York: Broadway Books. Fascinating history of the attempts to collect brains of successful people and try to relate their brain anatomy to their success.

Klawans, H. L. (1988). *Toscanini's fumble and other tales of clinical neurology.* Chicago: Contemporary Books. Description of illustrative cases of brain damage and their behavioral consequences.

Chapter 4

An enormous amount of brain development occurs by the time a child is 1 year old.

(Source: Dr. Dana Copeland)

Genetics, Development, and Plasticity

Chapter Outline

Module 4.1
Genetics and Evolution of Behavior
Mendelian Genetics
Heritability
The Evolution of Behavior
In Closing: Genes and Behavior

Module 4.2
Development of the Brain
Maturation of the Vertebrate Brain
Pathfinding by Axons
Determinants of Neuronal Survival
The Vulnerable Developing Brain
Differentiation of the Cortex
Fine-Tuning by Experience
In Closing: Brain Development

Module 4.3
Plasticity after Brain Damage
Brain Damage and Immediate Treatments
Later Mechanisms of Recovery
In Closing: Brain Damage and Recovery

Learning Objectives

After studying this chapter, you should be able to:

1. Distinguish between genetic and epigenetic influences on development.
2. Describe the types of evidence researchers use to infer heritability.
3. Explain why heritability varies from one population to another.
4. Explain why high heritability does not mean that the environment cannot change something.
5. Describe ways in which genetic variations can influence behavior.
6. Give examples of evolutionary explanations in psychology.
7. Discuss the problems in explaining a possible evolutionary basis for altruistic behavior.
8. Describe the early development of the brain.
9. Discuss the formation of new neurons in a mature brain.
10. Describe the evidence showing that axons seek specific targets.
11. Define apoptosis, and explain how neurotrophins prevent it.
12. Cite examples of how experiences alter brain anatomy and function.
13. Evaluate explanations of risky behavior in adolescents.
14. List possible mechanisms of recovery after brain damage.
15. Explain how remodeling in the cerebral cortex produces the phantom limb experience.

"Some assembly required." Have you ever bought a package with those ominous words? Sometimes, all you have to do is attach a few parts, but other times, you face page after page of confusing instructions.

The human nervous system requires an enormous amount of assembly, and the instructions are unlike those for the objects we assemble from a kit. Instead of "Put this piece here and that piece there," the instructions are, "Put these axons here and those dendrites there, and then wait to find out what happens. Keep the connections that work the best and discard the others. Continue making new connections and keeping only the successful ones."

Therefore, we say that the brain's anatomy is *plastic*. It continues changing throughout life.

Module 4.1

Genetics and Evolution of Behavior

Learning Objectives

After studying this module, you should be able to:

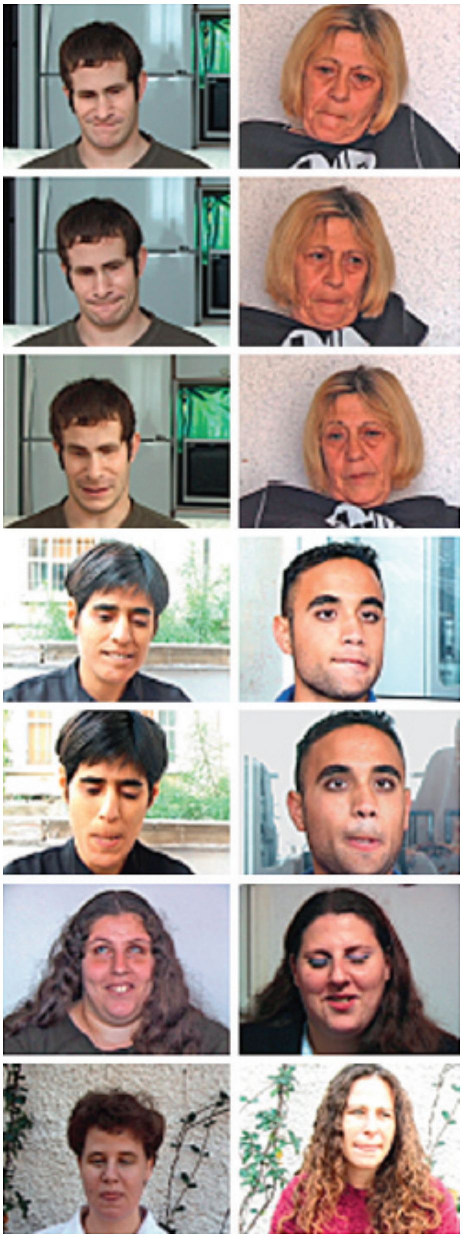
1. Distinguish between genetic and epigenetic influences on development.
2. Describe the types of evidence researchers use to infer heritability.
3. Explain why heritability varies from one population to another.
4. Explain why high heritability does not mean that the environment cannot change something.
5. Describe ways in which genetic variations can influence behavior.
6. Give examples of evolutionary explanations in psychology.
7. Discuss the problems in explaining a possible evolutionary basis for altruistic behavior.

Everything you do depends on both your genes and your environment. Consider facial expressions. A contribution of the environment is obvious: You smile more when your life is going well and frown when things are going badly. Does heredity influence your facial expressions? Researchers examined facial expressions of people who were born blind and therefore could not have learned to imitate facial expressions. Their facial expressions were remarkably similar to those of their sighted relatives, as shown in Figure 4.1 (Peleg et al., 2006).

Controversies arise when we move beyond the generalization that both heredity and environment are important. For example, to what extent do differences in human intelligence depend on genetic differences or environmental influences? Similar questions arise for sexual orientation, alcoholism, weight gain, mental illness, and much more. This module should help you understand the issues, even when the answers remain debatable. We begin with a review of genetics.

Figure 4.1 Facial expressions by people born blind (left) and their sighted relatives (right)

The similarities imply a genetic contribution to facial expressions.



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Mendelian Genetics

Prior to the work of Gregor Mendel in the late 19th century, scientists thought that inheritance was a blending process in which the properties of the sperm and the egg simply mixed, like two colors of paint.

Mendel's results demonstrated that inheritance occurs through **genes**, units of heredity that maintain their structural identity from one generation to another. Most genes come in pairs because they are aligned along **chromosomes** (strands of genes) that come in pairs. An exception to this rule is that a male mammal has unpaired X and Y chromosomes. Classically, a gene has been defined as part of a chromosome, which is composed of the double-stranded molecule **deoxyribonucleic acid (DNA)**. However, genes do not always have the discrete locations we once imagined (Bird, 2007). Several genes might overlap on a stretch of chromosome. Sometimes a genetic outcome depends on parts of two or more chromosomes. Sometimes one part of a chromosome alters the expression of another part.

A strand of DNA serves as a template (model) for the synthesis of **ribonucleic acid (RNA)** molecules, a single-strand chemical. One type of RNA molecule—messenger RNA—serves as a template for the synthesis of protein molecules. DNA contains four "bases": adenine, guanine, cytosine, and thymine. The order of those bases determines the order of corresponding bases along an RNA molecule: adenine, guanine, cytosine, and uracil. The order of bases along an RNA molecule in turn determines the order of amino acids that compose a protein. For example, if three RNA bases are in the order cytosine, adenine, and guanine, then the protein adds the amino acid *glutamine.* If the next three RNA bases are uracil, guanine, and guanine, the next amino acid is *tryptophan*. Any protein consists of some combination of 20 amino acids. It's an amazingly simple code, considering the complexity of body structures and functions that result from it.

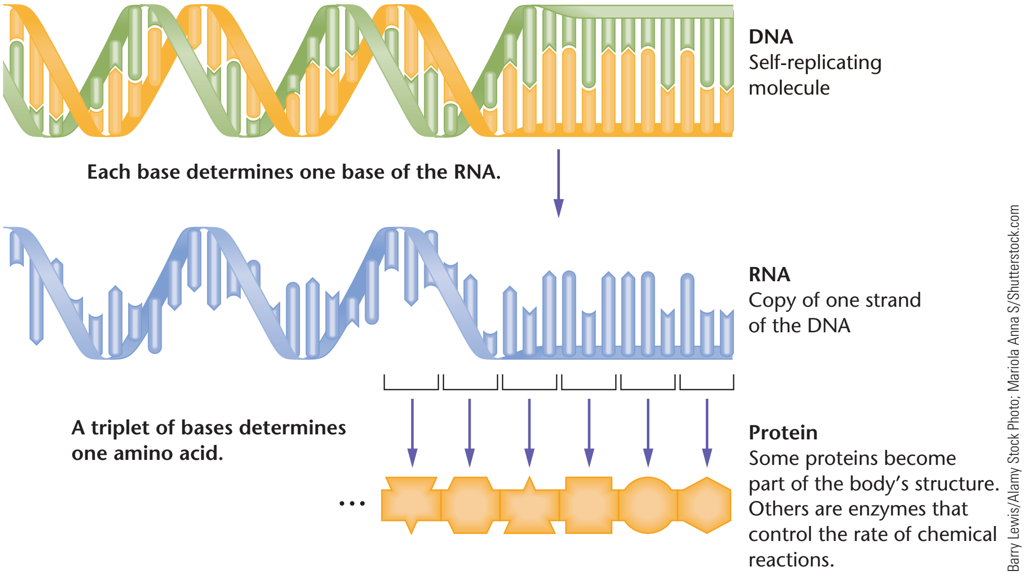
Figure 4.2 summarizes the main steps in translating information from DNA through RNA into proteins. Some proteins form part of the structure of the body. Others serve as *enzymes*, biological catalysts that regulate chemical reactions in the body. Not all RNA molecules code for proteins. Many RNA molecules perform regulatory functions.

If you have the same gene on your two chromosomes, you are **homozygous** for that gene. If you have an unmatched pair of genes, you are **heterozygous** for the gene. For example, you might have a gene for blue eyes on one chromosome and a gene for brown eyes on the other.

Genes are dominant, recessive, or intermediate. A **dominant gene** exerts a strong effect in either the homozygous or heterozygous condition. A **recessive gene** exerts its effects only in the homozygous condition. For example, a gene for brown eyes is dominant and a gene for blue eyes is recessive. In someone with one gene for brown eyes and one for blue, the result is brown eyes. The gene for high sensitivity to the taste of phenylthiocarbamide (PTC) is dominant, and the gene for low sensitivity is recessive. Only someone with two recessive genes has trouble tasting it (Wooding et al., 2004). Figure 4.3 illustrates the possible results of a mating between people who are both heterozygous for the PTC-tasting gene. Because each has one high taste sensitivity gene—let's abbreviate it "T"—both parents readily taste PTC. Each parent transmits either a high taste sensitivity gene (T) or a low taste sensitivity gene (t) to any child. Therefore, a child in this family has a 25 percent chance of two T genes, a 50 percent chance of the heterozygous condition, and a 25 percent chance of being homozygous for the t gene.

Figure 4.2 How DNA controls development of the organism

The sequence of bases along a strand of DNA determines the order of bases along a strand of RNA. RNA in turn controls the sequence of amino acids in a protein molecule.


DNA
Self-replicating molecule
Each base determines one base of the RNA.
RNA
Copy of one strand of the DNA
A triplet of bases determines one amino acid.
…
Protein
Some proteins become part of the body's structure. Others are enzymes that control the rate of chemical reactions.

Barry Lewis/Alamy Stock Photo; Mariola Anna S/Shutterstock.com

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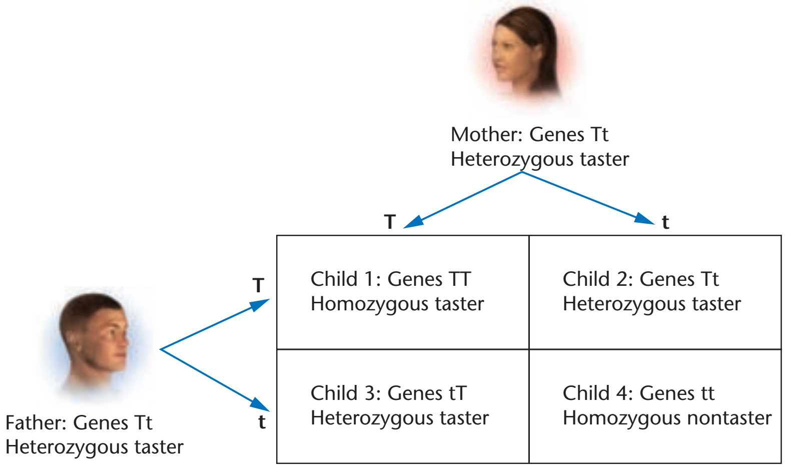
Figure 4.3 Four equally likely outcomes of a mating between parents who are heterozygous for a given gene (Tt)

A child in this family has a 25 percent chance of being homozygous for the dominant gene (TT), a 25 percent chance of being homozygous for the recessive gene (tt), and a 50 percent chance of being heterozygous (Tt).



Courtesy of the Archives, California Institute of Technology

However, an example like this can be misleading, because it implies that a single gene produces a single outcome. Even in the case of eye color, that is not true. Researchers have identified at least 10 genes that contribute to variations in eye color (Liu et al., 2010), and at least 700 genes that contribute to differences in people's height (Marouli et al., 2017). Each gene that contributes to eye color or height affects other characteristics as well. Furthermore, changes in the environment can increase or decrease the expression of a gene. Genetic influences are more complex than we once imagined.

Stop & Check

1. Suppose you have high sensitivity to tasting PTC. If one of your parents can also taste it easily, what (if anything) can you predict about your other parent's ability to taste it?
2. Suppose you have high sensitivity to the taste of PTC. If one of your parents has low sensitivity, what (if anything) can you predict about your other parent's taste sensitivity?
3. Why is it misleading to talk about "a gene for" some characteristic?

See page 115 for the answer.

Sex-Linked and Sex-Limited Genes

The genes on the sex chromosomes (designated X and Y in mammals) are known as **sex-linked genes**. All other chromosomes are autosomal chromosomes, and their genes are known as **autosomal genes**.

In mammals, a female has two X chromosomes, whereas a male has an X and a Y. During reproduction, the female necessarily contributes an X chromosome, and the male contributes either an X or a Y. If he contributes an X, the offspring is female; if he contributes a Y, the offspring is male. (Here we are talking about genetic sex. Psychological gender identification is another matter.)

When biologists speak of sex-linked genes, they usually mean X-linked genes. The small Y chromosome has a gene that causes the testes to form, but not as many genes as the X chromosome. It also has sites that influence the functioning of genes on other chromosomes.

One human X-linked gene controls red-green color vision (Figure 4.4). A man with the recessive form of this gene on his X chromosome is red-green color deficient because he has no other X chromosome. A woman is color deficient only if she has that recessive gene on both of her X chromosomes. So, for example, if 8 percent of human X chromosomes contain the gene for color vision deficiency, then 8 percent of men will be color deficient, but less than 1 percent of women will be (0.08 × 0.08).

Distinct from sex-linked genes are the **sex-limited genes**, present in both sexes but active mainly in one sex. Examples include the genes that control the amount of chest hair in men, breast size in women, amount of crowing in roosters, and rate of egg production in hens. Both sexes have the genes, but sex hormones activate them in one sex and not the other, or one sex more than the other. Many sex-limited genes show their effects at puberty.

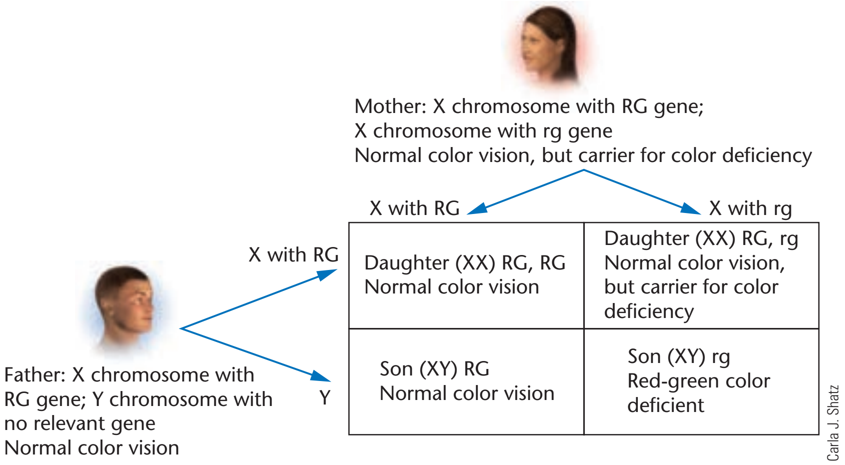
Stop & Check

4. How does a sex-linked gene differ from a sex-limited gene?

See page 115 for the answer.

Figure 4.4 Red-green color deficiency, a sex-linked gene

RG represents normal red-green color vision, and rg represents red-green color deficiency. Any son who receives an rg gene from his mother is red-green color deficient, because the Y gene has no gene for color vision. A daughter could be color deficient only if her father has color deficiency and her mother is a carrier for the condition.


Mother: X chromosome with RG gene;
X chromosome with rg gene
Normal color vision, but carrier for color deficiency
X with RG
X with rg
X with RG
Y
Father: X chromosome with RG gene; Y chromosome with no relevant gene
Normal color vision
Daughter (XX) RG, RG
Normal color vision
Daughter (XX) RG, rg
Normal color vision, but carrier for color deficiency
Son (XY) RG
Normal color vision
Son (XY) rg
Red-green color deficient

Carla J. Shatz

Genetic Changes

Genes change in several ways. One way is by **mutation**, a heritable change in a DNA molecule. Changing a DNA base to any of the other three types means that the mutant gene will code for a protein with a different amino acid at one location in the molecule. Given that evolution has already had eons to select the best makeup of each gene, most mutations are harmful, except when the environment changes. For example, a mutation in a gene controlling the immune system might provide better protection against a new virus. A mutation is possible whenever a cell divides, not just at the time of conception. Because some mutations occur as an embryo is developing or later, what we call "identical" twins can have genetic differences (D'Gama and Walsh, 2018).

Another way to change genes is by duplication or deletion. During the process of reproduction, part of a chromosome that ordinarily appears once might instead appear twice or not at all. When this process happens to a tiny portion of a chromosome, we call it a microduplication or microdeletion. Because microduplications provide new material for genetic change, they have been a necessary part of our evolutionary history. However, most cases of microduplication or microdeletion are harmful.

Epigenetics

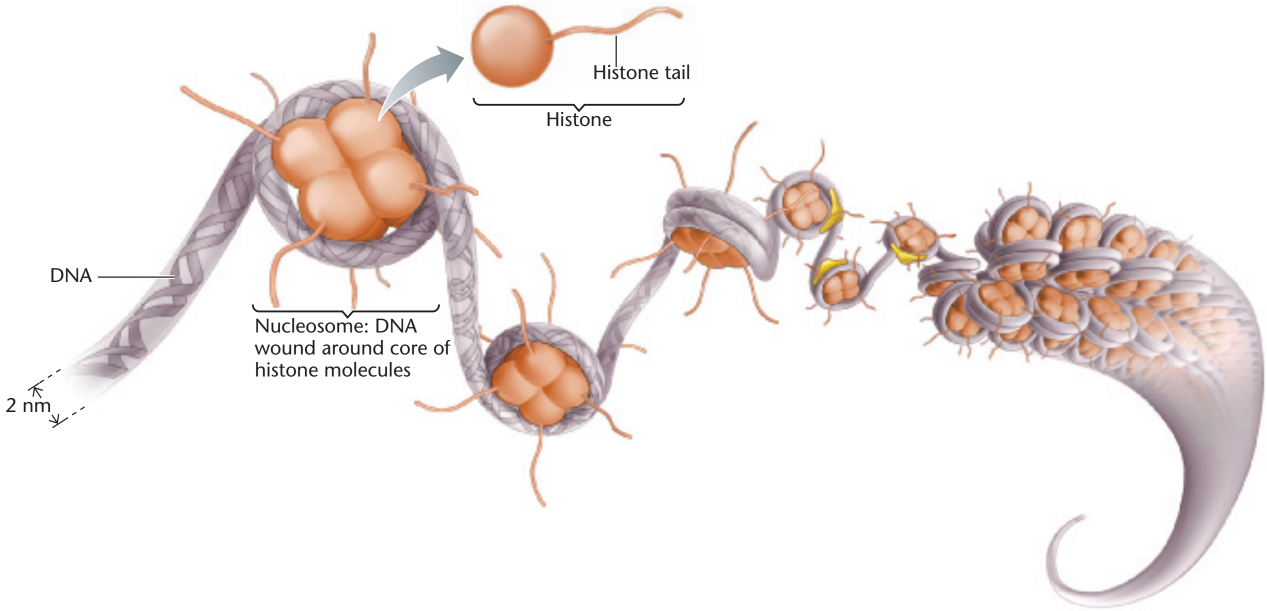
The field of **epigenetics** deals with changes in gene expression. The genes that are most active in your brain are not the same as those active in your lungs or kidneys, and those that are most active in one part of your brain may not be the most active in another part. Many genes that are essential to a developing fetus become less active after birth, and others that did little for the fetus become important later (Hannon et al., 2016; Jaffe et al., 2016). Many genes increase their activity at puberty (Lomniczi et al., 2013). For psychology, the important aspect of epigenetics is that experiences can produce epigenetic changes, altering gene expression in the brain.

Many illustrations of the DNA molecule, as in Figure 4.2, show it as a straight line, which is an oversimplification. In fact, proteins called **histones** bind DNA into a shape that is more like string wound around balls (Figure 4.5). To activate a gene, the DNA must partially unwind from the histones. Adding an acetyl group ($COCH_3$) to a histone tail loosens the histone's grip on the DNA, facilitating the expression of the genes. Removing an acetyl group tightens the histone's grip on the DNA and silences the gene. Another epigenetic change is to add a methyl group (CH_3) at the beginning of a gene, turning it off, or removing a methyl group to turn it on (Tsankova et al., 2007).

Many experiences can alter the chemistry of the brain in a way that activates some genes and inactivates others. So far, most of the research has dealt with laboratory rodents. Exposing a pregnant mouse to alcohol changes the brain epigenetics of her offspring (Mews et al., 2019). If a mother rat is malnourished during pregnancy, her offspring alter the expression of certain genes to conserve energy and adjust to a world in which food will presumably be hard to find. If rich food becomes abundant later in life, an offspring's gene expressions predispose it to overeating, obesity, and heart disease (Godfrey et al., 2007). Epigenetic changes can be inherited, at least for a generation or two. When mice were conditioned to fear a particular odor, the first and second generations of offspring showed increased sensitivity to that odor (Dias and Ressler, 2014).

Figure 4.5 DNA bound into a ball shape by histone proteins

When an acetyl group attaches to a loose end of a histone molecule, it loosens the histone's grip on DNA, exposing more genes to the possibility of being active.



Erich Hartmann/Magnum Photos

When male mice were exposed to chronic stressful experiences, their offspring showed a weakened hormonal response to stresses and altered gene expression in part of the brain. The effect was traced to RNA molecules in the father's sperm (Rodgers et al., 2015).

In humans, drug addiction produces epigenetic changes in the brain (Sadri-Vakili et al., 2010; Tsankova et al., 2007). Severe traumatic experiences in early childhood decrease methylation of many brain genes, increasing the later risk of depression or posttraumatic stress disorder (Klengel et al., 2013). The experience of feeling socially isolated or rejected alters the activity of hundreds of genes (Slavich and Cole, 2013). How well your grandparents were nourished or malnourished in childhood correlates with your chances for a long, healthy life (Pembrey et al., 2006).

The general point is that what you do at any moment not only affects you now but also produces epigenetic effects that alter gene expression for later. The distinction between "genetic" effects and "experiential" effects has become blurry. Experiences act by altering the activity of genes.

Stop & Check

5. How does an epigenetic change differ from a mutation?
6. How does adding a methyl or acetyl group to a histone protein alter gene activity?

See page 115 for the answer.

Heritability

Does your singing ability depend more on your heredity or environment? That question as stated is meaningless. Unless you had both heredity and environment, you couldn't sing at all. Rephrasing the question makes it meaningful: Do the observed *differences* among individuals depend more on *differences* in heredity or *differences* in environment? If you sing better than someone else, the reason could be different genes, better training, or both. If the variation depends largely on genetic differences, the characteristic has high **heritability**. Heritability ranges from zero, indicating no genetic contribution to the variation, to one, indicating complete control.

How could we determine the heritability of a characteristic? Researchers have relied mostly on studies of twins, supplemented by studies of adopted children. They compare **monozygotic** ("from one egg") **twins** and **dizygotic** ("from two eggs") **twins**. Most people call monozygotic twins "identical," a misleading term because the twins can differ, sometimes because of mutations that happened after conception. Still, monozygotic twins originated from a single fertilized egg, and if they resemble each other more than dizygotic twins in some regard, the resemblance implies a genetic contribution. Researchers sometimes also examine "virtual twins"—children of the same age, adopted at the same time into a single family. They grow up in the same environment from infancy, but without any genetic similarity. Any similarities in behavior imply environmental influences (Segal, 2000).

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A second kind of evidence is studies of adopted children. A resemblance between adopted children and their biological parents suggests a hereditary influence. However, the biological mother contributes not only her genes but also the prenatal environment. Health, diet, and smoking and drinking habits during pregnancy can influence the child's development.

Based on twin studies and adoption studies, researchers have found evidence for significant heritability of almost every behavior they have tested, including ability to postpone gratification (Sanchez-Roige et al., 2018), childhood misbehavior (Burt, 2009), cognitive performance (Plomin et al., 2013), drawing style (Arden et al., 2014), educational success (J. Lee et al., 2018), empathy (Abramson et al., 2020), loneliness (McGuire and Clifford, 2000), neuroticism (Lake et al., 2000), risk taking (Rao et al., 2018), sleep quality (Madrid-Valero et al., 2020), social attitudes (Posner et al., 1996), speed of learning a second language (Dale et al., 2010), television watching (Plomin et al., 1990), verbal fluency (T. Lee et al., 2018), and enjoyment of nature walks (Chang et al., 2022). About the only behavior that has *not* shown a significant heritability is religious affiliation, such as Protestant or Catholic (Eaves et al., 1990).

A heritability estimate shows how much something depends on variations in heredity within a population, and it varies from one population to another. For example, consider alcohol abuse. If all families within a population have similar attitudes toward alcohol use, heritability could be high. If some families have strict rules and others are lenient, the environmental influence is stronger, and therefore heritability will be lower.

Although a heritability estimate is interesting, it is more useful to know which genes are important for an outcome, and how those genes exert their effects. Modern methods make it possible to identify specific genes. Using the *candidate gene* approach, researchers test a hypothesis, such as "a gene that increases the activity of the serotonin transporter may be linked to an increased risk of depression." Another approach, a *genome wide association study*, examines the entire set of chromosomes while comparing two groups, such as people with and without depression. Because that approach tests a huge number of hypotheses at once (one for each gene), it has a risk of seeing an apparent effect by accident. To avoid an accidental finding, the researchers need to set an unusually high standard for statistical significance, and therefore they need to test tens or hundreds of thousands of people.

One problem in interpreting the results is the overlap between hereditary and environmental influences. Certain genes are known to be associated with greater educational success, but mothers with more of those genes tend to maintain better health and nutrition during pregnancy, and therefore what appears to be an inherited influence is also partly an environmental influence (Armstrong-Carter et al., 2020).

Stop & Check

7. What are the main types of evidence to estimate the heritability of some behavior?
8. If every child had an equally good environment, would heritability of IQ scores increase or decrease? If every child had an equally bad environment, would heritability increase or decrease?
9. What would be the heritability of having two arms? High or low?

See page 115 for the answer.

Environmental Modification

Even a trait with high heritability can be modified by environmental interventions. A prime example is **phenylketonuria** (FEE-nil-KEET-uhn-YOOR-ee-uh), or **PKU**, a genetic inability to metabolize the amino acid phenylalanine. If PKU is not treated, phenylalanine accumulates to toxic levels, impairing brain development and leaving a child cognitively impaired, restless, and irritable. Approximately 1 percent of Europeans carry a recessive gene for PKU. Fewer Asians and almost no Africans have the gene (T. Wang et al., 1989).

Although PKU is a hereditary condition, environmental interventions can modify it. Physicians in many countries routinely test the level of phenylalanine or its metabolites in each baby's blood. If a baby has high levels, indicating PKU, physicians advise the parents to put the baby on a strict low-phenylalanine diet to protect the brain (Waisbren et al., 1994). The success of this diet shows that *heritable* does not mean *unmodifiable.*

A couple of notes about PKU: The required diet is difficult. People need to avoid meats, eggs, dairy products, grains, and especially aspartame (NutraSweet), which is 50 percent phenylalanine. Instead, they eat an expensive formula containing the other amino acids. Physicians formerly believed that children with PKU could quit the diet after a few years. Later experience has shown that high phenylalanine levels remain dangerous throughout life. A woman with PKU should be especially careful during pregnancy and when nursing. Even a genetically normal baby cannot handle the enormous amounts of phenylalanine that an affected mother might pass through the placenta or milk.

Stop & Check

10. What example illustrates the point that even if some characteristic is highly heritable, a change in the environment can alter it?

See page 115 for the answer.

How Genes Influence Behavior

A gene can influence brain development, but it can influence behavior even without being expressed in the brain.

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Suppose your genes make you unusually attractive. As a result, strangers smile at you and people want to get to know you. If their reactions influence your personality, then your genes altered your behavior by altering your environment.

Now imagine a child born with genes promoting greater than average height and running speed. Because of these factors, the child shows early success at basketball, and soon spends more and more time playing basketball. As a result, the child spends less time than average on other pursuits—watching videos, playing chess, or anything else. The point is that genes can influence behavior in roundabout ways. We should not be surprised that nearly every human behavior has some heritability.

The Evolution of Behavior

Charles Darwin, known as the founder of evolutionary theory, didn't like the term *evolution.* He preferred *descent with modification*, emphasizing the idea of changes without necessarily implying improvement. **Evolution** is a change over generations in the frequencies of various genes in a population.

We distinguish two questions about evolution: How *did* some species evolve, and how *do* species evolve? To ask how a species did evolve is to ask what evolved from what. For example, because humans are more similar to chimpanzees and bonobos than to other species, biologists infer a common ancestor. As new evidence becomes available, biologists often change their opinions about the evolutionary relationship between one species and another.

In contrast, the question of how species *do* evolve is a question of how the process works, and that process is a necessary outcome from what we know about reproduction. The reasoning goes as follows:

- Because of genetic influences, offspring generally resemble their parents. That is, "like begets like."
- Mutations, recombinations, and microduplications of genes introduce new heritable variations that help or harm an individual's chance of surviving and reproducing.
- Certain individuals reproduce more than others do, thus passing on their genes to the next generation. Any gene that is associated with greater reproductive success will become more prevalent in later generations. Therefore, the current generation of any species resembles the individuals who reproduced in the past. If a change in the environment causes a different gene to increase the probability of survival and reproduction, then that gene will spread in the population.

Because plant and animal breeders have long understood this idea, they choose individuals with a desired trait and make them the parents of the next generation through a process called **artificial selection**. Over many generations, breeders have produced exceptional racehorses, chickens that lay huge numbers of eggs, hundreds of breeds of dogs, and so forth. Darwin's (1859) insight was that nature also selects. If certain individuals are more successful than others in finding food, escaping enemies, resisting illness, attracting mates, or protecting their offspring, then their genes will become more prevalent in later generations. Given enough time, this process can produce the variety of life that we observe. Note that the phrase "survival of the fittest" is misleading. What matters most is not survival, but reproduction.

Misunderstandings about Evolution

Let's clarify the principles of evolution by addressing a few misconceptions:

- *Does the use or disuse of a structure or behavior cause an evolutionary increase or decrease in that feature?* You may have heard people say something like, "Because we hardly ever use our little toes, they get smaller and smaller in each succeeding generation." This idea is a carryover of biologist Jean-Baptiste Lamarck's theory of evolution through the inheritance of acquired characteristics, known as **Lamarckian evolution**. According to this idea, if you exercise your arm muscles, your children will be born with bigger arm muscles, and if you fail to use your little toes, your children's little toes will be smaller than yours. Biologists have found no mechanism for Lamarckian evolution to occur and no evidence that it does. People's little toes will shrink in future generations only if people with genes for smaller little toes reproduce more than average.

一对夫妇只生一个孩子
护

Barry Lewis/Alamy Stock Photo

From 1980 to 2016, China limited each family to one child. Any enforced limitation of family size decreases genetic differences in reproduction.

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- *Have humans stopped evolving?* Because modern medicine can keep almost anyone alive, and because welfare programs in prosperous countries provide the necessities of life for almost everyone, some people assert that human evolution has slowed or stopped.

  The flaw in this argument is that evolution depends on reproduction, not just survival. If some people have more children than others, their genes will spread in the population.
- *Does "evolution" mean "improvement"?* It depends on what you mean by "improvement." By definition, evolution improves **fitness**, which is operationally defined as *the number of copies of one's genes that endure in later generations.* If you have more children than average, and they survive long enough to reproduce, you are evolutionarily fit, regardless of whether you are successful in any other way. You also increase your fitness by supporting your relatives, who spread many of your genes by their own reproduction. However, genes that increase fitness at one time and place might be disadvantageous after a change in the environment. For example, the colorful tail feathers of the male peacock enable it to attract females but they might become disadvantageous in the presence of a new predator that responds to bright colors. The genes of the current generation evolved because they were fit for *previous* generations. They may or may not be adaptive in the future.
- *Does evolution benefit the individual or the species?* Neither: It benefits the genes! In a sense, you don't use your genes to reproduce yourself. Your genes use *you* to reproduce *themselves* (Dawkins, 1989). If a gene that causes you to risk your life to protect your children, you may leave behind more surviving children than you would have otherwise, and if so, that gene will increase in prevalence.

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Sometimes a sexual display, such as a peacock's spread of its tail feathers, improves reproductive success and spreads the associated genes. In a changed environment, this gene could become maladaptive.

Natural selection cannot favor a gene that benefits the species while disadvantaging the individuals with the gene. Some people have claimed that when lemming populations become too high, some of the lemmings jump off cliffs to decrease the overpopulation problem. If that were true (and it is not!), the next generation would all descend from lemmings that failed to jump. A "self-sacrificing" gene would die out with those who had it.

Stop & Check

11. Many people believe the human appendix is useless. Will it become smaller and smaller with each generation?

See page 115 for the answer.

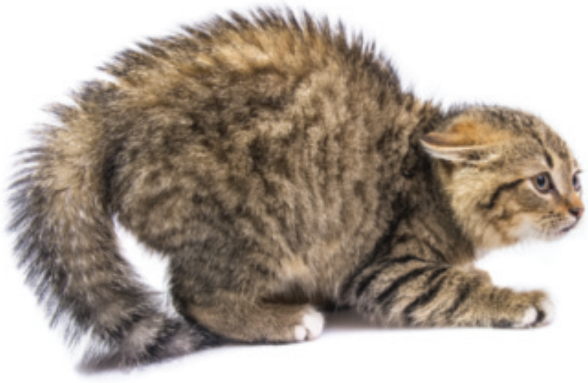
Evolutionary Psychology

Evolutionary psychology concerns how behaviors evolved. It emphasizes *evolutionary* and *functional* explanations—that is, how our genes reflect those of our ancestors and why natural selection might have favored genes that promote certain behaviors. The assumption is that any behavior characteristic of a species must have provided an advantage, at least in ancestral times.

Several human behaviors make no sense except in terms of evolution. For example, people get "goose bumps"—erections of the hairs, especially on their arms and shoulders—when they are cold or frightened. Goose bumps produce little if any benefit to humans because our shoulder and arm hairs are short and usually covered by clothing. In most other mammals, however, erected hairs make a frightened animal look larger and more intimidating (Figure 4.6). They also provide extra insulation when

Figure 4.6 A frightened cat with erect hairs

For animals with long hairs, erecting those hairs increases insulation from cold and makes the animal look larger and more dangerous. We humans continue to erect our hairs in those same situations as a remnant from our evolutionary past.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the air is cold. We explain human goose bumps by saying that the behavior evolved in our remote ancestors and we inherited the mechanism.

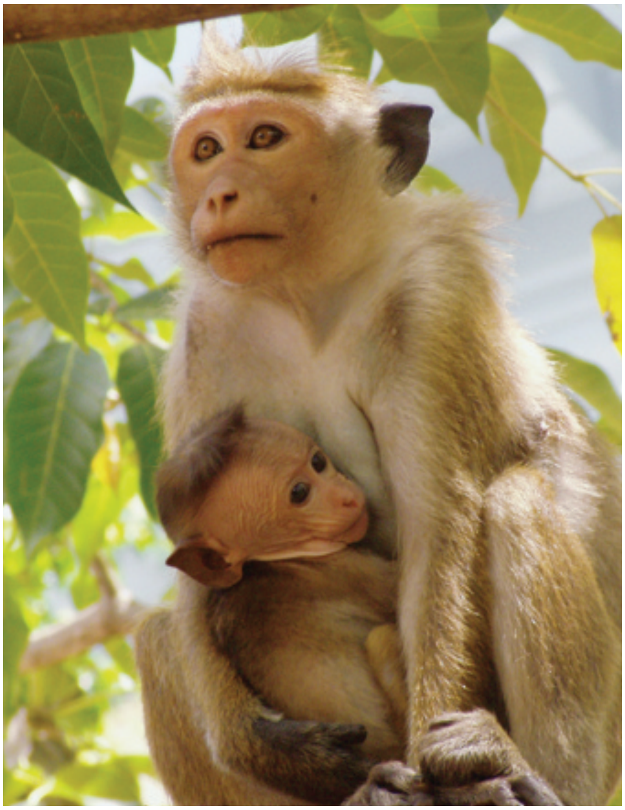
Also consider the infant grasp reflex (Figure 4.7). An infant will grasp tightly onto a finger or similar object in the palm of the hand. What good does that accomplish? For our monkey-like ancestors, it was critical. A mother monkey often needs all four limbs to search for food or to escape from a predator. An infant monkey that couldn't hold on would jeopardize its life.

You might be curious about what happens to the infant grasp reflex. It gradually fades in strength over the first few months of life, but it is never erased from the nervous system. Rather, as the frontal cortex develops, it inhibits the grasp reflex. The reflex returns after damage to the frontal cortex. It also returns temporarily after carbon dioxide, morphine, alcohol, or other substances sufficiently inhibit the frontal cortex (Richter and Hines, 1932; Richter and Paterson, 1932). The next time you are with someone who is, um, "chemically impaired," you might put a pencil or finger in the palm of that person's hand and see whether you can elicit an infant grasp reflex.

Try It Yourself

Figure 4.7 Grasp reflex in human and monkey infants

The grasp reflex, which accomplishes little or nothing for human infants, makes sense as an evolutionary remnant of a behavior necessary for the survival of our monkey-like ancestors.



Jo Ellen Kalat

Here is another example of an evolutionary explanation, this time relating to old age: Throughout the animal kingdom, and for plants as well, life does not outlast the capacity to reproduce. Consider salmon: After they return to their breeding grounds to spawn, they stop eating and soon die. Living after you stop reproducing is disadvantageous from an evolutionary standpoint, because you would be competing with your offspring for food and shelter. One exception to that rule is human females. Women go through menopause and stop reproducing around age 50, on average, but they are likely to live for decades after that—in fact, longer than men, who have at least a small potential for reproduction even in old age. An explanation is what is called the *grandmother effect*. In times and places where infant survival was less certain than it is in prosperous countries today, having a grandmother nearby, especially the mother's mother, significantly increased the infant's chances for survival (Engelhardt et al., 2019). (Grandfathers are sometimes useful too, but they are less dependable.)

To further illustrate evolutionary psychology, consider the theoretically interesting example of **altruistic behavior**, an action that benefits someone other than the actor. When you engage in altruistic behavior, you help other individuals survive and spread their genes, at a possible cost to yourself. Could a gene that encourages altruism spread, and if so, how?

Altruism, in the sense of helping a nonrelative without getting something in return, is uncommon in the animal kingdom (Cheney, 2011). Even when animals do appear altruistic, they often have a selfish motive. When a crow finds food on the ground, it caws loudly, attracting other crows that will share the food. Altruism? Not really. A bird on the ground is vulnerable to attack by cats and other enemies. Having other crows around means more eyes to watch for dangers.

Also consider meerkats (a kind of mongoose). Periodically, one or another member of a meerkat colony stands and, if it sees danger, it emits an alarm call (Figure 4.8). The alarm call helps the others (including its relatives), but nevertheless the one who sees the danger first and emits the alarm call is the one most likely to escape (Clutton-Brock et al., 1999).

Still, humans do show altruistic behavior, at least sometimes. We contribute to charities. We help people in distress. You might explain something to a classmate who is competing for a good grade in a course. Some people donate a kidney to save the life of someone they didn't even know (MacFarquhar, 2009). For the sake of

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Figure 4.8 Sentinel behavior: Altruistic or not?

As in many other prey species, meerkats sometimes show sentinel behavior in watching for danger and warning the others. However, the meerkat that emits the alarm is the one most likely to escape the danger.

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illustration, let's suppose—without evidence—that a gene increases altruistic behavior. Could it spread within a population? One common reply is that most altruistic behaviors cost very little. True, but costing little is not good enough. A gene spreads only if the individuals with it reproduce more than those without it. Another common reply is that the altruistic behavior benefits the species. True again, but the rebuttal is the same. A gene that fails to help the individual will not spread in the population.

A better explanation is **kin selection**—selection for a gene that benefits the individual's relatives. A gene spreads if it causes you to take great efforts to protect your children, because they share many of your genes, including perhaps a gene for protecting their own children. Natural selection can also favor altruism toward other relatives (Dawkins, 1989; Hamilton, 1964; Trivers, 1985). If you have genes that promote helpfulness toward your relatives, the behavior might generalize toward nonrelatives, especially if they resemble your relatives in some way (Bowles and Posel, 2005; Krakauer, 2005).

Another explanation is **reciprocal altruism**, the idea that individuals help those who will probably return the favor. You would help someone who helped you in the past, and maybe also someone whom you observed being helpful to a third person. Even young children show this tendency (Martin and Olson, 2015). The idea is not just "you scratched my back, so I'll scratch yours," but also "you scratched someone else's back, so I'll scratch yours." Anyone who helps others builds a good reputation. This system works only if individuals recognize one another. Otherwise, an uncooperative individual can accept favors, prosper, and never repay the favors. In other words, reciprocal altruism requires an ability to identify individuals and remember them later. Humans, of course, are excellent at recognizing one another.

A third hypothesis is **group selection**. According to this idea, altruistic groups thrive better than less cooperative ones (Bowles, 2006; Kohn, 2008). Altruistic groups do have an advantage, but the idea of group selection has been controversial for this reason: Wouldn't an uncooperative individual within the cooperative group gain an advantage? Theorists have concluded that group selection does work under certain circumstances, such as when cooperative individuals do most of their interactions with one another (Simon et al., 2013). Group selection works well for humans, because of our ability to punish or expel uncooperative people.

At its best, evolutionary psychology leads to research that helps us understand a behavior. The search for a functional explanation directs researchers to explore species' different habitats and ways of life until we understand why they behave differently. The approach is criticized when its practitioners propose speculative explanations without supporting evidence (Schlinger, 1996).

Stop & Check

12. What are plausible ways for possible altruistic genes to spread in a population?

See page 115 for the answer.

Module 4.1 | In Closing

Genes and Behavior

In the control of behavior, genes are important but not all-important. Certain behaviors have a high heritability, such as the ability to taste PTC. Many other behaviors are influenced by genes but also subject to strong influence by experience. Our genes and our evolution make it possible for humans to be what we are today, but they also give us the flexibility to change our behavior as circumstances warrant.

Studying the genetics of behavior is more difficult with humans than with laboratory animals, because researchers have such limited control over environmental influences and no control over who mates with whom. Inferring how human behavior evolved is also difficult, because we do not know enough about the lives of our ancient ancestors. Nevertheless, in spite of the difficulties, these interesting questions attract much research interest.

Summary

1. Genes are chemicals that maintain their integrity from one generation to the next and influence the development of the individual. A dominant gene affects development regardless of whether a person has pairs of that gene or only a single copy per cell. A recessive gene affects development only in the absence of the dominant gene. **105**
2. Genes can change by mutations, microduplications, and microdeletions. **107**
3. Gene expression can change in a process called epigenetics, as chemicals activate or deactivate parts of chromosomes. Experiences can cause epigenetic changes, and in some cases an epigenetic change can influence the next generation. **107**
4. Most behavioral variations reflect the combined influences of genes and environmental factors. Heritability is an estimate of the amount of variation that is due to genetic variation as opposed to environmental variation. **108**
5. Researchers estimate heritability of a human condition by comparing monozygotic and dizygotic twins, supplemented by comparing adopted children to their biological and adoptive parents. **108**
6. Researchers try to identify the genes responsible for particular behavioral tendencies. **109**
7. Even if a behavior shows high heritability for a given population, a change in the environment might significantly alter the behavioral outcome. **109**
8. Genes influence behavior directly by altering brain chemicals and indirectly by affecting other aspects of the body. **109**
9. The process of evolution through natural selection is a necessary outcome, given what we know about reproduction: Mutations sometimes occur in genes, and individuals with certain sets of genes reproduce more successfully than others do. **110**
10. Evolution spreads the genes of the individuals who have reproduced the most. Therefore, if some heritable characteristic is widespread within a population, it is reasonable to look for ways in which that characteristic is or has been adaptive. **111**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

altruistic behavior **112**
artificial selection **110**
autosomal genes **106**
chromosomes **105**
deoxyribonucleic acid (DNA) **105**
dizygotic twins **108**
dominant gene **105**
epigenetics **107**
evolution **110**
evolutionary psychology **111**
fitness **111**
genes **105**
group selection **113**
heritability **108**
heterozygous **105**
histones **107**
homozygous **105**
kin selection **113**
Lamarckian evolution **110**
monozygotic twins **108**
mutation **107**
phenylketonuria (PKU) **109**
recessive gene **105**
reciprocal altruism **113**
ribonucleic acid (RNA) **105**
sex-limited genes **106**
sex-linked genes **106**

Thought Questions

1. For what human behaviors, if any, are you sure that heritability would be extremely low?
2. Certain genes influence the probability of developing Alzheimer's disease or other conditions that occur mostly in old age. Given that the genes controlling old age have their onset long after people have stopped having children, how could evolution have any effect on such genes?

Stop & Check Answers

1. If one parent has high sensitivity to the taste of PTC, we can make no predictions about the other parent. You may have inherited a high-sensitivity gene from one parent, and because the gene is dominant, you need only one copy of the gene to taste PTC.
2. If one parent has low sensitivity, you must have inherited your high-sensitivity gene from the other parent, who must have high sensitivity.
3. Almost any characteristic depends on more than one gene, as well as influences from the environment.
4. A sex-linked gene is on the X or Y chromosome. A sex-limited gene is on an autosomal chromosome, but hormones activate it in one sex more than the other.
5. A mutation is a permanent change in part of a chromosome. An epigenetic change is an increase or decrease in the activity of a gene or group of genes.
6. Adding a methyl group turns genes off. An acetyl group loosens histone's grip and increases gene activation.
7. The main evidence is greater similarity between monozygotic twins than dizygotic twins. Another is resemblance between adopted children and their biological parents.
8. If the quality of the environment is equal for all, heritability will *increase*, regardless of whether the environment is equally good or equally bad. If everyone has the same environment, whatever variation still exists would have to be due to heredity.
9. The heritability is almost zero. You may be surprised, because having two arms is obviously under genetic control. However, heritability measures how much the *variation* in some feature depends on *variation* in genetics. Nearly all the variation in having two arms or having fewer depends on amputations (under the control of the environment) and not on any variation in genetics.
10. Keeping a child with the PKU gene on a strict low-phenylalanine diet prevents the cognitive deficits that the gene ordinarily causes. The general point is that sometimes a highly heritable condition can be modified environmentally.
11. No, the appendix will shrink only if people with a gene for a smaller appendix reproduce more successfully than other people do.
12. Altruistic genes could spread because they facilitate care for one's kin or because they facilitate exchanges of favors with others (reciprocal altruism). Group selection may also work under some circumstances, especially if the cooperative group has a way to punish or expel an uncooperative individual.

Module 4.1 | End-of-Module Quiz

1. Under what condition would the effects of a recessive gene become evident?
   - a. Only if someone is heterozygous for the gene
   - b. Only if someone is homozygous for the gene
   - c. Always, regardless of whether someone is heterozygous or homozygous
   - d. Never

2. If both parents have low sensitivity to the taste of PTC, what can we predict about their children?
   - a. All of them will have high sensitivity to PTC.
   - b. All of them will have low sensitivity to PTC.
   - c. About one-fourth of them will have low sensitivity to PTC.
   - d. About one-fourth of them will have high sensitivity to PTC.

3. What is a sex-limited gene?
   - a. A gene that influences sexual behavior
   - b. A gene with greater effects on one sex than the other
   - c. A gene on either the X or Y chromosome
   - d. A gene that becomes activated during sexual behavior

4. What does a microdeletion remove?
   - a. Part of a protein
   - b. Part of a brain wave
   - c. Part of a chromosome
   - d. Part of a neuron

5. What does an epigenetic change do?
   - a. It duplicates or deletes part of a chromosome.
   - b. It increases or decreases the probability of a mutation.
   - c. It increases or decreases the expression of a gene.
   - d. It changes the frequency of a gene in an entire population.

6. Dizygotic twins resemble each other genetically by the same amount as what?
   - a. Monozygotic twins
   - b. Brother and sister
   - c. Father and mother
   - d. Cousins

7. Why does a genome wide association study have the risk of an accidental finding?

- **a.** It deals with a nonrepresentative sample of the population.
- **b.** It relies on inaccurate measurements.
- **c.** It tests many hypotheses at once.
- **d.** It publishes data before they have been peer-reviewed.

8. Heritability of some trait would probably be highest for which of the following?

- **a.** A community in which a few families control most of the wealth
- **b.** An isolated community with much in-breeding
- **c.** A community that provides an equally supportive environment for all
- **d.** A community with much variation in diet

9. Which of the following offers strong evidence that environmental changes can largely counteract the effect of a gene?

- **a.** The effects of temperature on children with autism spectrum disorder
- **b.** The effects of diet on children with phenylketonuria (PKU)
- **c.** The effects of muscle training on children who have suffered a concussion
- **d.** The effects of sleep on children with malaria

10. In evolutionary terms, which of the following people is the most “fit”?

- **a.** The one who lives the longest
- **b.** The one who accumulates the most wealth
- **c.** The one with the most children and grandchildren
- **d.** The one who remains healthiest throughout life

11. What, if anything, can we predict about the future of human evolution?

- **a.** People will get smarter, wiser, and more cooperative.
- **b.** People will not change, because evolution no longer affects humans.
- **c.** People will become more like whichever people tend to have the most children.
- **d.** We cannot make any of these predictions.

12. Why would a gene favoring altruism be difficult to explain?

- **a.** It would seem not to benefit the species.
- **b.** It would have to alter brain functioning.
- **c.** It benefits someone other than the individual.
- **d.** It would probably have other effects also.

Answers: 1b, 2b, 3b, 4c, 5c, 6b, 7c, 8c, 9b, 10c, 11c, 12c.

Module 4.2

Development of the Brain

Learning Objectives

After studying this module, you should be able to:

8. Describe the early development of the brain.
9. Discuss the formation of new neurons in a mature brain.
10. Describe the evidence showing that axons seek specific targets.
11. Define apoptosis, and explain how neurotrophins prevent it.
12. Cite examples of how experiences alter brain anatomy and function.
13. Evaluate explanations of risky behavior in adolescents.

Think of all the things you can do that you couldn't have done a few years ago—analyze statistics, read a foreign language, write brilliant critiques of complex issues, and more. Have you developed these skills because of brain growth? No, your dendrites have grown new branches, but your brain as a whole hasn't grown.

Now think of all the things that 1-year-old children can do that they could not do at birth. Have *they* developed their new skills because of brain growth? To a large extent, yes, although the way the brain grew depended on experiences. In this module, we consider how neurons develop, how their axons connect, and how experience modifies development.

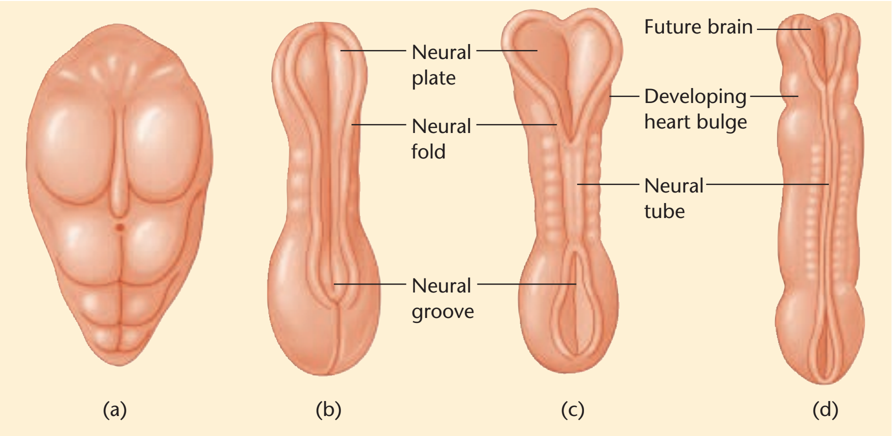
Maturation of the Vertebrate Brain

The earliest stages of development are similar across species. A series of genes known as *homeobox genes*—found in vertebrates, insects, plants, and even fungi and yeast—regulate the expression of other genes and control the start of anatomical development, including which end is the front and which is the rear. All the homeobox genes share a large sequence of DNA bases. A mutation in one of them causes insects to form legs where their antennas should be, or to form an extra set of wings. In humans, mutations in homeobox genes have been linked to serious mental and physical disorders (Conti et al., 2011).

The human central nervous system begins to form when the embryo is about 2 weeks old. The dorsal surface thickens, and then long thin lips rise, curl, and merge, forming a neural tube that surrounds a fluid-filled cavity (Figure 4.9). As the tube sinks under the surface of the skin, the forward end enlarges and differentiates into the

Figure 4.9 Early development of the human central nervous system

The brain and spinal cord begin as folding lips surrounding a fluid-filled canal. The stages shown occur at approximately 2 to 3 weeks after conception.



tomas del amo/Alamy Stock Photo

hindbrain, midbrain, and forebrain (Figure 4.10). The other end becomes the spinal cord. The fluid-filled cavity within the neural tube becomes the central canal of the spinal cord and the four ventricles of the brain, containing the cerebrospinal fluid (CSF). The first muscle movements start at age 7½ weeks, driven by spontaneous activity in the spinal cord, while the sensory organs are not yet functional (Provine, 1972). That is, contrary to what we might guess, movements start before sensations.

Newborn human brains weigh about 350 grams. By the end of the first year, they weigh around 1,000 g, close to the adult average of 1,200 to 1,400 g. In early infancy, the primary sensory areas of the cortex—responsible for registering vision, hearing, and other senses—are more mature than the prefrontal cortex and other areas responsible for attention, memory, and decision making. Those areas develop slowly, continuing through the teenage years and beyond (Alcuter et al., 2014; G. Li et al., 2014).

Growth and Development of Neurons

Neuroscientists distinguish several stages in the development of neurons. **Proliferation** is the production of new cells. Early in development, the cells lining the ventricles of the brain divide. Some cells remain where they are as **stem cells**, continuing to divide, whereas others migrate to other parts of the nervous system. In humans, most of the migration occurs before birth, but a small number continue to migrate for the first few months after birth (Paredes et al., 2016). One of the major differences between human brains and chimpanzee brains is that human neurons continue proliferating longer (Rakic, 1998; Vrba, 1998).

Early in development, the primitive cells, not yet identifiable as neurons or glia, begin to **migrate** (move). Chemicals known as *immunoglobulins* and *chemokines* guide neuron migration. A deficit in these chemicals leads to impaired migration, decreased brain size, and intellectual impairment (Berger-Sweeney and Hohmann, 1997; Crossin and Krushel, 2000; Tran and Miller, 2003). The brain has many kinds of immunoglobulins and chemokines, reflecting the complexity of brain development.

As a cell **differentiates** into a neuron, it begins to form its dendrites, axon, and synapses. Figure 4.11 shows the expansion of dendritic trees for neurons in the prefrontal cortex, from birth to age 2½ years (Petanjek et al., 2008). By age 2½, these neurons are close to the adult anatomy. Neurons develop different anatomies and functions, based on when and where they developed, and what genes they express (Nowakowski et al., 2017).

Synaptogenesis, the formation of synapses, begins long before birth and continues throughout life, as neurons form new synapses and discard old ones. The process slows in older people, as does the formation of new dendritic branches (Buell and Coleman, 1981; Jacobs and Scheibel, 1993).

Figure 4.10 Human brain at four stages of development

The growing forebrain quickly surrounds the midbrain and part of the hindbrain.

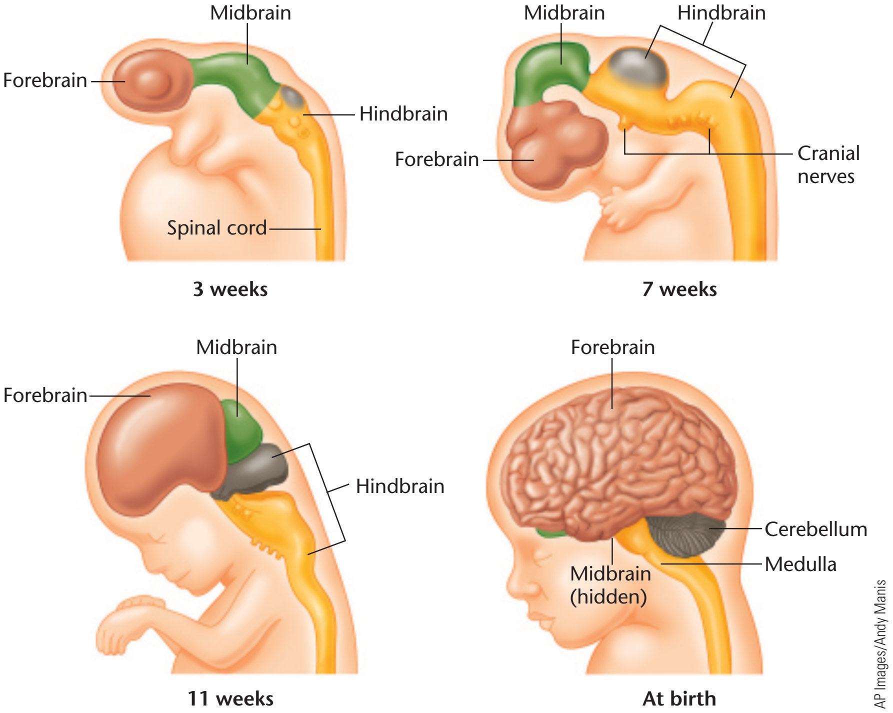


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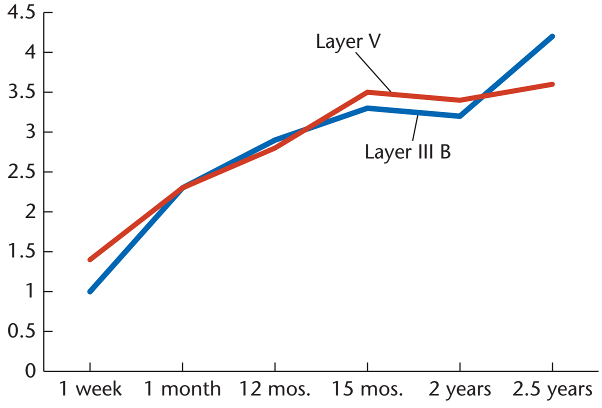
Figure 4.11 Total length of dendrites in two layers of prefrontal cortex from birth to age 2½ in humans.

Dendrites develop rapidly at first. By age 2½ they are close to the adult pattern.



Source: Based on data of Petanjek et al. (2008)

A slower stage of neuronal development is **myelination**, the process by which glia produce the insulating fatty sheaths that accelerate transmission in many vertebrate axons. Myelin forms first in the spinal cord and then in the hindbrain, midbrain, and forebrain. Myelination continues gradually throughout life and is modified by certain types of learning (Pease-Raissi and Chan, 2021).

Stop & Check

13. What causes the first muscle movements in a developing embryo?
14. Which comes first: migration, synaptogenesis, or myelination?

See page 133 for the answer.

New Neurons Later in Life

Can the adult vertebrate brain generate new neurons? The traditional belief, dating back to Cajal's work in the late 1800s, was that vertebrate brains formed all their neurons in embryological development or early infancy. Beyond that point, neurons could modify their shape, but the brain could not develop new neurons. For most of the brain, Cajal was right. However, researchers have discovered a few exceptions to the no-new-neurons rule.

The first exceptions were the olfactory receptors, which are exposed to the outside world and its toxic chemicals. The nose contains stem cells that remain immature throughout life. Periodically, they divide, with one cell remaining immature while the other differentiates to replace a dying olfactory receptor. This process continues for years, probably throughout life (Durante et al., 2020; Graziadei and deHan, 1973). In songbirds, one brain area that is necessary for singing loses neurons in fall and regains them the next spring (mating season) (Nottebohm, 2002; Wissman and Brenowitz, 2009).

How could researchers determine whether new neurons form in the adult human brain? A clever method relies on a radioactive isotope of carbon, ^{14}C. The concentration of ^{14}C in the atmosphere, compared with other isotopes of carbon, was nearly constant over time until the era of nuclear bomb testing released much radioactivity, including ^{14}C. That era ended with the Test Ban Treaty of 1963. The concentration of ^{14}C peaked in 1963 and has been declining since then. If you examine tree rings, you find that a ring that formed in 1963 has the ^{14}C content typical of 1963, a ring that formed in 1990 has the ^{14}C content typical of 1990, and so forth. Researchers examined carbon in the DNA of various human cells. Every cell acquires DNA molecules when it forms and keeps them until it dies. When researchers examined people's skin cells, they found a concentration of ^{14}C corresponding to the year in which they did the test. That is, skin cells turn over rapidly, and your skin cells are less than a year old. When they examined skeletal muscle cells, they found a ^{14}C concentration corresponding to 15 years ago, indicating that skeletal muscles are replaced slowly, making the average cell 15 years old. Cells of the heart are, on average, almost as old as the person, indicating that the body replaces no more than 1 percent of heart cells per year (Bergmann et al., 2009). When researchers examined neurons in the cerebral cortex (of dead people at autopsy), they found a ^{14}C concentration corresponding to the year of the person's birth. These results indicate that the cerebral cortex forms no new neurons after the year of birth (Spalding et al., 2005).

What about other parts of the brain? In many mammals, new small interneurons form throughout life in the hippocampus, an important area for memory formation (Song et al., 2002; van Praag et al., 2002). A supply of new neurons keeps the hippocampus "young" for learning new tasks (Ge et al., 2007; Schmidt-Hieber et al., 2004).

Ah, but what is true for "many mammals" may not be true for humans. New neurons can be found in the human hippocampus up to about age 7 (Sorrells et al., 2018), but beyond that age, some research methods have found evidence for new neurons and other methods have not (Denoth-Lippuner and Jessberger, 2021). One study applied a single procedure to the adult hippocampus of several species, finding the largest number of new neurons in mice, fewer in pigs and macaque monkeys, and either none or almost none in humans. Of the more than 171,000 human neurons examined, only two appeared to be possibly immature, developing neurons (Franjic et al., 2022).

Stop & Check

15. New receptor neurons form in which sensory system?
16. What evidence demonstrates that new neurons do not form in the human cerebral cortex?

See page 133 for the answer.

Pathfinding by Axons

If you asked someone to run a cable from one place to another in your room, your directions could be simple. But imagine asking someone to run a cable to somewhere on the other side of the country. You would have to give detailed instructions about how to find the right city, the right building, and the location within the building. The developing nervous system faces a similar challenge when it sends axons over great distances. How do they find their way?

Pathfinding by Axons

Biologist Paul Weiss (1924) conducted an experiment in which he grafted an extra leg to a salamander and then waited for axons to grow into it. Unlike mammals, salamanders and other amphibians accept transplants of extra limbs and generate new axon branches to the extra limbs. Much research requires finding the right species to study. After the axons reached the muscles, the extra leg moved in synchrony with the normal leg next to it.

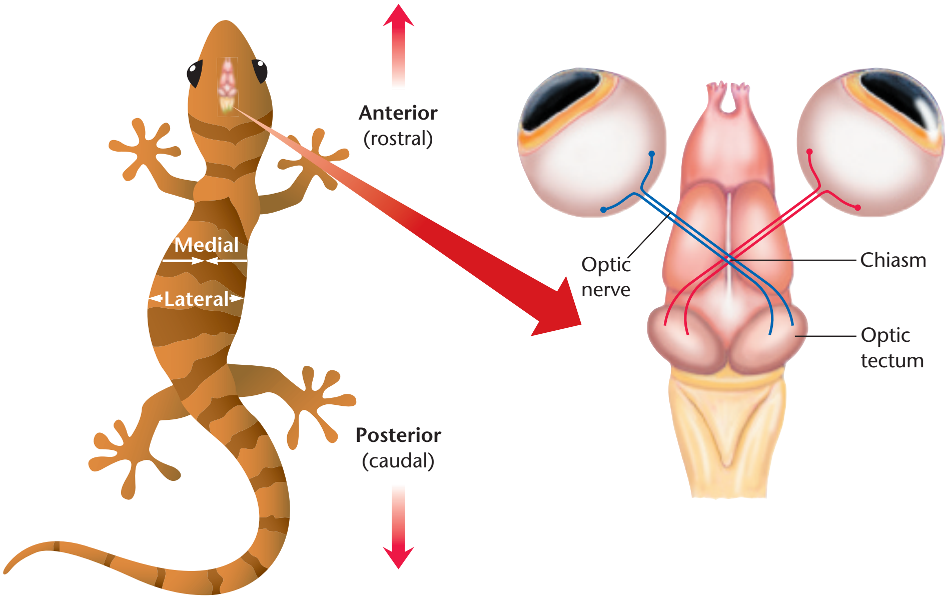
Weiss dismissed the idea that each axon found its way to the correct muscle in the extra limb. He suggested instead that the nerves attached to muscles at random and then sent a variety of messages, each one tuned to a different muscle. He supposed that muscles were like radios tuned to different stations: Each muscle received many signals but responded to only one. (The 1920s were the early days of radio, and it was an appealing analogy to think the nervous system might work like a radio. Today we compare the nervous system to computers, the most advanced technology of our era.)

Later evidence supported the interpretation that Weiss had rejected: The salamander's extra leg moved in synchrony with its neighbor because each axon found the correct muscle. Roger Sperry, a former student of Weiss, performed a classic experiment that showed how sensory axons find their way to their correct targets. Sensory axons find their way in the same manner that axons to the muscles find their way. First, Sperry cut the optic nerves of some newts. (Note the importance of choosing the right species: A cut optic nerve grows back in amphibians, but not in mammals or birds.) The damaged optic nerve grew back and connected with the *tectum*, which is amphibians' main visual area (Figure 4.12), thereby reestablishing normal vision. So then Sperry's question was: Did they grow at random, or did they grow to a specific target?

For the next set of newts, Sperry (1943) cut the optic nerve and then rotated the eye by 180 degrees. When the axons grew back to the tectum, the axons from what had originally been the dorsal portion of the retina (which was now ventral) grew back to the area responsible for vision in the dorsal retina. Axons from other parts of the retina also grew back to their original targets. The newt now saw the world upside down and reversed, responding to stimuli in the sky as if they were on the ground and to stimuli on the left as if they were on the right (Figure 4.13). Each axon regenerated to the same place where it had originally been, presumably by following a chemical trail.

Figure 4.12 Connections from eye to brain in a newt

The optic tectum is a large structure in fish, amphibians, reptiles, and birds. Note: Connections from eye to brain in a newt differ from those in a human, as described in the module on lateralization.



(**Source:** From Romer, 1962)

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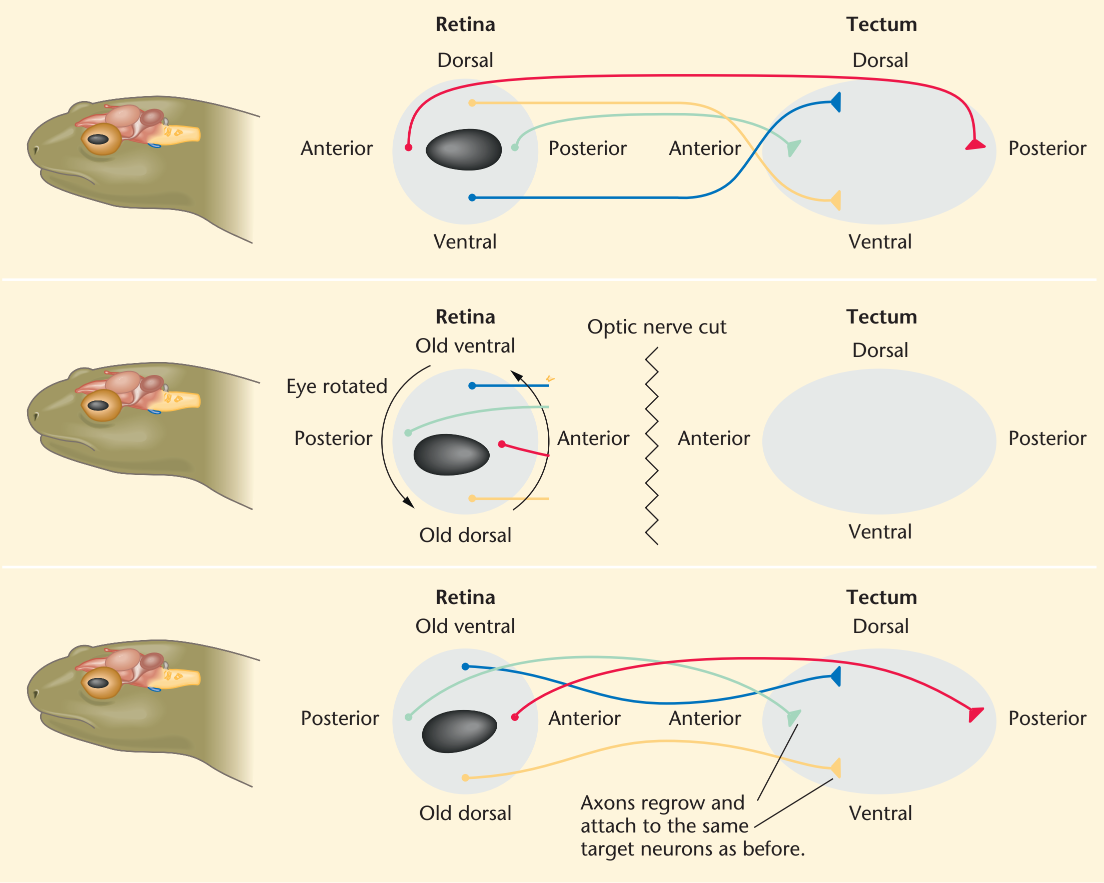
Figure 4.13 Sperry's experiment on nerve connections in newts

After he cut the optic nerve and inverted the eye, the axons grew back to their original targets, not to the targets corresponding to the eye's current position.

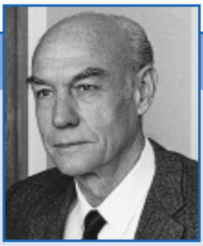

Retina
Dorsal
Anterior
Posterior
Ventral
Tectum
Dorsal
Anterior
Posterior
Ventral
Retina
Old ventral
Eye rotated
Posterior
Anterior
Old dorsal
Optic nerve cut
Tectum
Dorsal
Anterior
Posterior
Ventral
Retina
Old ventral
Posterior
Anterior
Old dorsal
Tectum
Dorsal
Anterior
Posterior
Ventral
Axons regrow and
attach to the same
target neurons as before.

The next question was: How does an axon find its target? A growing axon follows a path of cell surface molecules, attracted by certain chemicals and repelled by others, in a process that steers the axon in the correct direction (Hiesinger, 2021). An additional factor is timing. Development proceeds by waves, as each type of neuron forms over a few days. Those that form earlier extend their axons longer and form more branches, thus making synapses with more targets. Those forming later connect to relatively few targets. Furthermore, neurons maturing at a particular time will make synapses with other neurons maturing at that time.

Stop & Check

17. What was Sperry's evidence that axons grow to a specific target instead of attaching at random?

See page 133 for the answer.


Courtesy of the Archives, California Institute of Technology

Roger W. Sperry (1913–1994)

> When subjective values have objective consequences . . . they become part of the content of science. . . . Science would become the final determinant of what is right and true, the best source and authority available to the human brain for finding ultimate axioms and guideline beliefs to live by, and for reaching an intimate understanding and rapport with the forces that control the universe and created man. (Sperry, 1975)

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Competition among Axons

When axons reach their targets, chemical gradients steer them to approximately their correct location, but they cannot achieve perfect accuracy. In fact, if a neuron cannot find its normal target (perhaps because that target has been damaged), in many cases it forms synapses onto some other target. You can think of it like dating: If you can't find your perfect mate, then you might attach to the best person available.

Each axon forms synapses onto many cells in approximately the correct location, and each target cell receives synapses from many axons. Over time, each postsynaptic cell strengthens the most appropriate synapses and eliminates others (Hua and Smith, 2004). This adjustment depends on the pattern of input from incoming axons (Catalano and Shatz, 1998). For example, one part of the thalamus receives input from many retinal axons. During embryological development, before the first exposure to light, repeated waves of spontaneous activity sweep over the retina from one side to the other. Consequently, axons from adjacent areas of the retina send almost simultaneous messages to the visual area of the thalamus. Each thalamic neuron selects a group of axons that are simultaneously active. In this way, it finds receptors from adjacent regions of the retina and rejects synapses from other locations (Meister et al., 1991).

These results suggest a general principle, called **neural Darwinism** (Edelman, 1987). In the development of the nervous system, we start with more neurons and synapses than we can keep, and then a selection process keeps the most successful combinations of synapses and rejects others. The principle of competition is an important one, although we should use the analogy with Darwinian evolution cautiously. Mutations in the genes are random events, but neurotrophins steer new axonal branches and synapses in approximately the right direction.

Stop & Check

18. If axons from the retina were prevented from showing spontaneous activity during early development, what would be the probable effect on development of the thalamus?

See page 133 for the answer.

Determinants of Neuronal Survival

Each ganglion of the sympathetic nervous system has enough axons to supply all the muscles and glands in its area, with no axons left over. How does the match come out so exact? Long ago, one hypothesis was that the muscles sent chemical messages to tell the sympathetic ganglion how many neurons to form. Rita Levi-Montalcini was largely responsible for disconfirming this hypothesis.

Levi-Montalcini's early life would seem unfavorable for a scientific career. She was a young Italian Jewish woman during the Nazi era. World War II destroyed the Italian economy, and at the time almost everyone discouraged women from scientific or medical careers. She had to spend several years in hiding during the war, but she spent those years conducting research on development of the nervous system, as she described in her autobiography (Levi-Montalcini, 1988) and a later interview with Moses Chao (2010). She developed a love for research and eventually discovered that the muscles do not determine how many axons *form.* They determine how many *survive.*

Initially, the sympathetic nervous system forms far more neurons than it needs. When any of its neurons forms a synapse onto a muscle, that muscle delivers a protein called **nerve growth factor (NGF)** that promotes the survival and growth of the axon (Levi-Montalcini, 1987). An axon that does not receive NGF degenerates, and its cell body dies. That is, each neuron starts life with a "suicide program": If its axon does not connect to an appropriate postsynaptic cell by a certain age, the neuron kills itself through a process called **apoptosis**,[1] a programmed mechanism of cell death. (Apoptosis is distinct from *necrosis*, which is death caused by an injury or a toxic substance.) NGF cancels the program

Carla J. Shatz

Carla J. Shatz

The functioning of the brain depends on the precision and patterns of its neural circuits. How is this amazing computational machine assembled and wired during development? The biological answer is so much more wonderful than anticipated! The adult precision is sculpted from an early imprecise pattern by a process in which connections are verified by the functioning of the neurons themselves. Thus, the developing brain is not simply a miniature version of the adult. Moreover, the brain works to wire itself, rather than assembling itself first and then flipping a switch, as might happen in the assembly of a computer. This kind of surprise in scientific discovery opens up new vistas of understanding and possibility and makes the process of doing science infinitely exciting and fascinating. (Shatz, personal communication)

---

[1] Apoptosis is based on the Greek root *ptosis* (meaning "dropping"), which is pronounced TOE-sis. Therefore, many scholars insist that the second *p* in *apoptosis* should be silent, a-po-TOE-sis. Others argue that *helicopter* is also derived from a root with a silent *p* (*pteron*), but we pronounce the *p* in *helicopter*, so we should also pronounce the second *p* in *apoptosis.* Most people today pronounce the second *p*, but be prepared for either pronunciation.

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for apoptosis; it is the postsynaptic cell's way of telling the incoming axon, "I'll be your partner. Don't kill yourself." You can think of it as dating with a deadline.

When the sympathetic nervous system begins sending axons toward the muscles and glands, it doesn't know the exact size of the muscles or glands. It makes more neurons than necessary and discards the excess, thereby achieving a match between axons and targets. In fact, all areas of the developing nervous system make more neurons than will survive into adulthood. Each brain area has a period of massive cell death, becoming littered with dead and dying cells (Figure 4.14) (Forger and Breedlove, 1987). This loss of cells is a natural part of development. In fact, loss of cells often indicates maturation. Maturation of successful cells is linked to simultaneous loss of less successful ones.

Nerve growth factor is a **neurotrophin**, meaning a chemical that promotes the survival and activity of neurons. (The word *trophin* derives from a Greek word for "nourishment.") In addition to NGF, the nervous system responds to *brain-derived neurotrophic factor* (BDNF) and several other neurotrophins (Airaksinen and Saarma, 2002). Neurotrophins are essential for growth of axons and dendrites, formation of new synapses, and learning (Alleva and Francia, 2009; Pascual et al., 2008; Rauskolb et al., 2010). Remember the term *BDNF*, because it becomes important again in the discussion of depression.

When cortical neurons reach a certain age in early development, a certain percentage of them die (Southwell et al., 2012). One factor controlling survival is that neurons need input from incoming axons. Researchers examined mice with a genetic defect that prevented release of neurotransmitters. The brains initially assembled normal anatomies, but then the neurons started dying rapidly (Verhage et al., 2000).

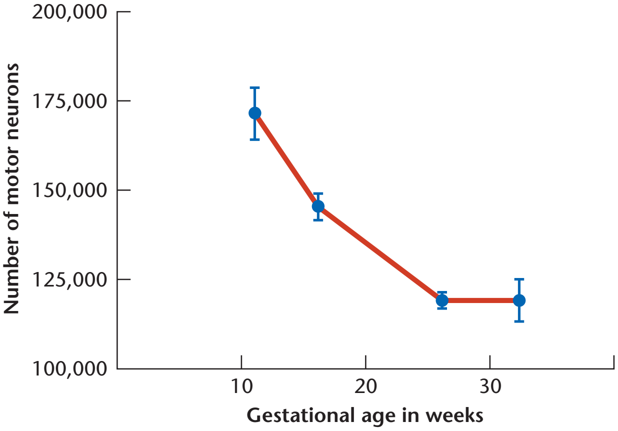
Stop & Check

19. What process assures that the spinal cord has the right number of axons to innervate all the muscle cells?
20. What class of chemicals prevents apoptosis in the sympathetic nervous system?
21. At what age does a person have the greatest number of neurons—during early development, during adolescence, or during adulthood?

See page 133 for the answer.

Figure 4.14 Cell loss during development of the nervous system

The number of motor neurons in the spinal cord of human fetuses is highest at 11 weeks and drops steadily until about 25 weeks. Axons that fail to make synapses die.



(**Source:** From "Motoneuronal death in the human fetus," by N. G. Forger and S. M. Breedlove, 1987, *Journal of Comparative Neurology, 264*, pp. 118–122. Copyright © 1987 Alan R. Liss, Inc. Reprinted by permission of N. G. Forger.)

The Vulnerable Developing Brain

According to Lewis Wolpert (1991), "It is not birth, marriage, or death, but gastrulation, which is truly the most important time of your life." Gastrulation is an early stage of embryological development. Wolpert's point was that if you mess up in early development, you have problems from then on. Actually, if you mess up during gastrulation, your life is over.

Early brain development is vulnerable to damage from malnutrition, toxic chemicals, and infections that would produce milder problems at later ages. A fever is a brief annoyance to an adult, but it impairs neuron proliferation in a fetus (Laburn, 1996). Malnutrition decreases an adult's pep, but before birth, it impairs brain development (Georgieff et al., 2018; Nelson et al., 2000). Exposure to bisphenol-A (BPA), a chemical used in producing plastics, is hazardous at any age, but especially while the brain is developing (Georgieff et al., 2018). Iron deficiency or impaired thyroid function produces lethargy in adults

Erich Hartmann/Magnum Photos

Rita Levi-Montalcini (1909–2012)

Many years later, I often asked myself how we could have dedicated ourselves with such enthusiasm to solving this small neuroembryological problem while German armies were advancing throughout Europe, spreading destruction and death wherever they went and threatening the very survival of Western civilization. The answer lies in the desperate and partially unconscious desire of human beings to ignore what is happening in situations where full awareness might lead one to self-destruction. (Levi-Montalcini, 1988, pp. 94–95)

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but intellectual deficits in infants. Thyroid deficiency was common in the past because of iodine deficiency. It is rare today because table salt is fortified with iodine. Exposure to lead is especially hazardous to a developing brain. People who were born in the United States from about 1951 to 1980 were exposed to much lead because of the widespread use of leaded gasoline in cars. People who grew up in areas with high levels of lead had greater risks of intellectual loss and neurotic personality problems (McFarland et al., 2022; Schwaba et al., 2021).

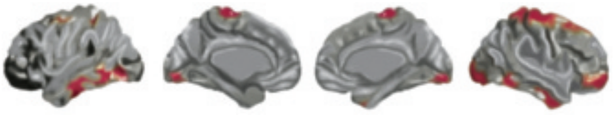
Many children of mothers who drink heavily during pregnancy are born with **fetal alcohol syndrome**, a condition marked by hyperactivity, impulsiveness, attention deficits, motor problems, heart defects, facial abnormalities, and sometimes thinning of the cerebral cortex (Zhou et al., 2011) (Figure 4.15). Even moderate drinking during pregnancy increases the risk of attention deficits, separation anxiety, and other problems (Eckstrand et al., 2012; Lees et al., 2020). However, a favorable environment after birth can reduce some of these difficulties.

Exposure to alcohol damages the brain in several ways. Early in pregnancy, it interferes with neuron proliferation. A little later, it impairs neuron migration and differentiation. Still later, it impairs synaptic transmission (Kleiber et al., 2013). Alcohol kills neurons partly by apoptosis. To prevent apoptosis, a brain neuron must receive input from incoming axons. Alcohol inhibits receptors for glutamate, the brain's main excitatory transmitter, and enhances receptors for GABA, the main inhibitory transmitter. Because of the decrease in net excitation, many neurons undergo apoptosis (Ikonomidou et al., 2000).

The developing brain is highly responsive to many influences from the mother. If a mother rat is exposed to stressful experiences, she becomes more fearful, she spends less than the usual amount of time licking and grooming her offspring, and her offspring become permanently more fearful in a variety of situations (Cameron et al., 2005). Analogously, the children of impoverished and abused women have, on average, increased problems in both their academic and social lives. The mechanisms in humans are not the same as those in rats, but the overall principles are similar: Stress to the mother changes her behavior in ways that change her offspring's behavior.

Figure 4.15 Cortical thinning as a result of prenatal alcohol exposure

The cortical areas marked in red are thinner, on average, in adults whose mothers drank alcohol extensively during pregnancy.



(**Source:** From "Developmental cortical thinning in fetal alcohol spectrum disorders," by D. Zhou et al., 2011, *NeuroImage, 58*, pp. 16–25.)

Stop & Check

22. Anesthetic drugs and anxiety-reducing drugs increase activity of GABA, decreasing brain excitation. It is possible that extensive exposure to such drugs before birth might interfere with brain development (Yu and Zhao, 2020). Based on what you just read, what is a possible reason for that concern?

See page 133 for the answer.

Differentiation of the Cortex

When and how does a neuron "decide" which kind of neuron it is going to be? It is not a sudden decision. Immature neurons experimentally transplanted from one part of the developing cortex to another develop the properties characteristic of their new location (McConnell, 1992), but neurons transplanted at a slightly later stage develop some new properties while retaining some old ones (Cohen-Tannoudji et al., 1994). It is like the speech of immigrant children: Those who enter a country when very young master the correct pronunciation, whereas older children retain an accent.

In one fascinating experiment, researchers explored what would happen to the immature auditory portions of the brain if they received input from the eyes instead of the ears. Ferrets—mammals in the weasel family—are born so immature that their optic nerves (from the eyes) have not yet reached the thalamus. On one side of the brain, researchers damaged the superior colliculus and the occipital cortex, the two main targets for the optic nerves. On that side, they also damaged the auditory input. Therefore, the optic nerve could not attach to its usual target, and the auditory area of the thalamus lacked its usual input. As a result, the optic nerve attached to what is usually the auditory area of the thalamus. What would you guess happened? Did the visual input cause auditory sensations, or did the auditory areas of the brain turn into visual areas?

The result was this: What would have been the auditory thalamus and cortex reorganized, developing some (but not all) of the characteristic appearance of visual areas (Sharma et al., 2000). How do we know whether the animals treated that activity as vision? Remember that the researchers performed these procedures on one side of the brain. They left the other side intact. The researchers presented stimuli to the normal side of the brain and trained the ferrets to turn one direction when they heard something and the other direction when they saw a light, as shown in Figure 4.16. After the ferrets learned this task well, the researchers presented a light that the rewired side could see. The result: The ferrets turned the way they had been taught to turn when they saw something. In short, the rewired temporal cortex, receiving input from the optic nerve, produced visual responses (von Melchner et al., 2000).

In a related study with newborn mice, researchers damaged the thalamic nucleus responsible for touch. As a result, axons from the nucleus responsible for pain sent their axons both to their usual target and to the cortical

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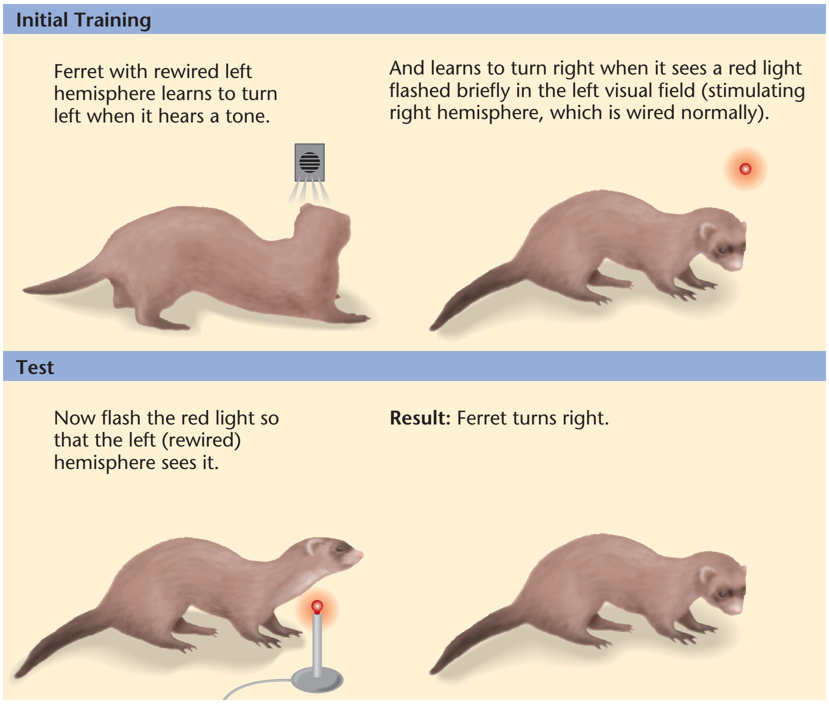
Figure 4.16 A ferret with rewired temporal cortex

First, the normal (right) hemisphere is trained to respond to a red light by turning to the right. Then, the rewired (left) hemisphere is tested with a red light. The fact that the ferret turns to the right indicates that it regards the stimulus as light, not sound.


Initial Training
Ferret with rewired left hemisphere learns to turn left when it hears a tone.
And learns to turn right when it sees a red light flashed briefly in the left visual field (stimulating right hemisphere, which is wired normally).
Test
Now flash the red light so that the left (rewired) hemisphere sees it.
Result: Ferret turns right.

area usually receptive to touch. The cortex then reorganized to be responsive to pain in both areas (Pouchelon et al., 2014). The overall conclusion is that to some extent, the sensory input instructs the cortex about how to develop.

Stop & Check

23. In the ferret study, how did the experimenters determine that visual input to the auditory portions of the brain produced a visual sensation?

See page 133 for the answer.

Fine-Tuning by Experience

The blueprints for a house determine its overall plan, but because architects cannot anticipate every detail, construction workers have to improvise. The same is true for your nervous system. Because of the unpredictability of life, our brains have evolved the ability to remodel themselves in response to experience (Shatz, 1992).

Experience and Dendritic Branching

Although the central structure of a dendrite becomes stable by adolescence, the peripheral branches of a dendrite remain flexible throughout life (Koleske, 2013). Dale Purves and R. D. Hadley (1985) injected a dye that let them watch the structure of a living mouse neuron over days or weeks. They found that some dendritic branches extended between one viewing and another, whereas others retracted or disappeared (Figure 4.17). About 6 percent of dendritic spines appear or disappear within a month (Xu et al., 2007). The gain or loss of spines means a turnover of synapses, which relates to learning (Yang et al., 2009).

Experiences guide the neuronal changes. Let's start with a simple example. Decades ago, it was typical for a laboratory rat to live alone in a small gray cage. Imagine by contrast several rats in a larger cage with a few objects to explore. Researchers called this an enriched environment, but it was enriched only by comparison to the deprived experience of a typical rat cage. A rat in the more stimulating environment developed a thicker cortex, more dendritic branching, and improved learning (Greenough, 1975; Rosenzweig and Bennett, 1996). As a result of this research, it has become more common to keep rats in a more enriched environment. A stimulating environment enhances sprouting of axons and dendrites in many other species also (Coss et al., 1980) (Figure 4.18).

We might suppose that the neuronal changes in an enriched environment depend on interesting experiences and social interactions. No doubt some of them do, but much of the enhancement produced by the enriched environment is due to physical activity. Using a running wheel improves neural plasticity and learning, even for rodents in social isolation (de Sousa Fernandes et al., 2020; Marlatt et al., 2012; Pietropaolo et al., 2006; van Praag et al., 1999).

Can we extend these results to humans? Physical activity is as beneficial for brain functioning in humans as in laboratory animals (de Sousa Fernandes et al., 2020). The results of enriched environments depend on what is compared to what. Remember, the studies with laboratory rats merely indicated that having a bigger cage with something to do was better than a small gray cage with nothing to do. So far as that goes, yes, humans in a normal environment do better intellectually than children in orphanages where the staff provides only minimum care (Helder et al., 2016; Loman et al., 2013). But the more important question is how much we could boost intelligence beyond normal by providing special training or greatly enhanced experiences.

Educators have long operated on the assumption that training children to do something difficult will enhance

Figure 4.17 Changes in dendritic trees of two mouse neurons

During a month, some branches elongated and others retracted.

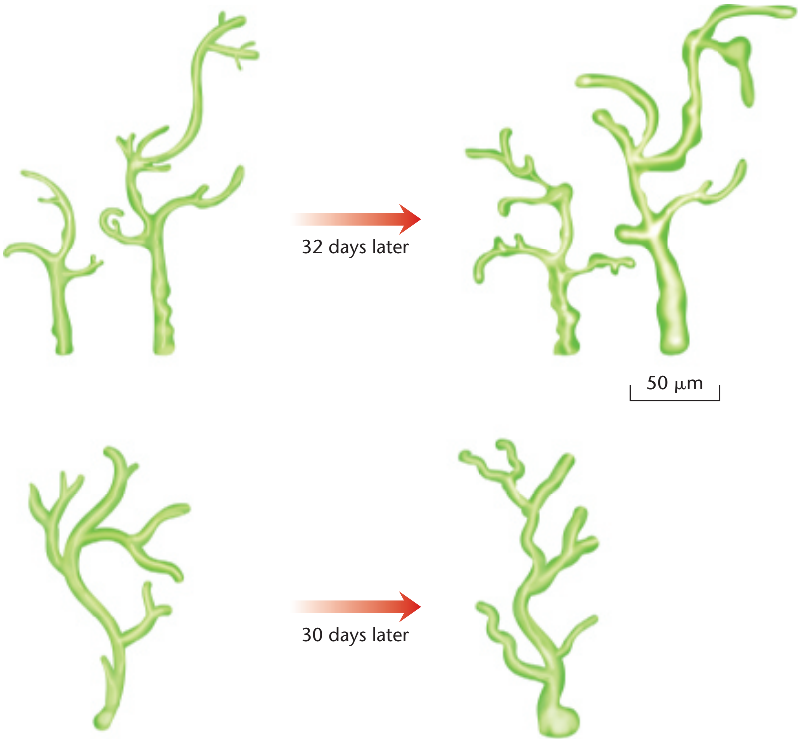


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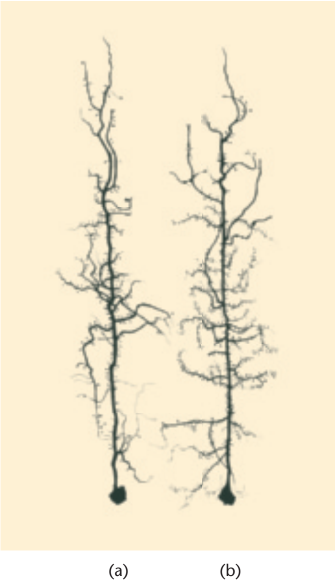
Figure 4.18 Effect of a stimulating environment

(a) A jewelfish reared in isolation develops neurons with fewer branches. (b) A fish reared with others has more dendritic branches.



(**Source:** Richard Coss)

their intellect. Long ago, British schools taught children Greek and Latin. Today it might be calculus, but in either case, the idea is to teach something challenging and hope students get smarter in other ways, too. The psychological term is **far transfer**. (*Near transfer* occurs if training on one task produces improvement on a similar task.) Far transfer is consistently a weak effect (Sala and Gobet, 2017). Many studies have attempted to improve memory or intelligence by computerized tasks that practice verbal and spatial skills. Despite high claims by the publishers of these programs, most studies find that users show benefits on the skills they practiced, but little improvement of anything else (Melby-Lervåg et al., 2016; Simons et al., 2016). Similarly, many people advise old people to do crossword puzzles or Sudoku puzzles to "exercise their brains." Experimental studies find that puzzle practice improves someone's skills at the puzzles, but not much else (Salthouse, 2006).

Stop & Check

24. An enriched environment promotes growth of axons and dendrites in laboratory rodents. What is known to be one important reason for this effect?

See page 133 for the answer.

Effects of Special Experiences

So far, generalized training programs to enhance overall intelligence have produced only temporary or modest benefits. However, prolonged practice of a particular activity does produce definite brain changes that enhance the ability to perform the task.

Brain Adaptations after Sensory Loss

What happens to the brain if one sensory system is impaired? For people who become blind early in life, the area in the temporal cortex that otherwise responds to visual motion becomes sensitive to the movement of sounds (Huber et al., 2019). Blind people are better than average at localizing sounds, if they are tested properly (Battal et al., 2020). Testing by asking them to point to the sound underestimates their skill, because blind people are not accustomed to pointing at anything.

The effect of blindness on touch depends on the task. Although many blind people have greater than average sensitivity in their fingers, they have just average sensitivity to touch on the lips and other areas to which they pay no more attention than anyone else (Wong et al., 2011).

In several studies, investigators asked sighted people and people who are blind since infancy to feel Braille letters or other objects and say whether two items were the same or different. On average, blind people performed more accurately than sighted people, as you would guess. The more interesting result was that brain scans on blind people during this task showed substantial activity in the occipital cortex, an area usually limited to visual information (Burton et al., 2002; Sadato et al., 1996, 1998). Evidently, touch information had invaded this cortical area.

To double-check this conclusion, researchers asked people to perform the same kind of task during temporary inactivation of the occipital cortex. Intense magnetic stimulation on the scalp temporarily inactivates neurons beneath the magnet. Applying this procedure to the occipital cortex of people who are blind interferes with their ability to identify Braille symbols, whereas it does not affect touch perception in sighted people. In short, blind people, unlike sighted people, use the occipital cortex to help identify what they feel (Cohen et al., 1997). In people who are blind since birth, the occipital cortex also responds to language and other auditory information (Bedny et al., 2015; Watkins et al., 2013).

Just as touch and sound come to activate what would be the visual cortex in blind people, touch and vision come to activate what would be the auditory cortex in deaf people (Karns et al., 2012). The increased representation of visual information enables deaf people to recognize emotional expressions better than average, and to detect stimuli in the visual periphery better than average. Still, the temporal cortex maintains features that would have been typical of the auditory cortex. Ordinarily, the auditory system locates sounds on the left-right axis more accurately than the up-down axis, and it is as sensitive to sounds in the periphery as to sounds straight ahead. After the auditory cortex reorganizes to attend to sight, it represents visual stimuli mainly on the left-to-right continuum, and it detects peripheral sights well instead of concentrating on the fovea, the way the visual cortex does (Almeida et al., 2018).

If someone were born without hands, and learned to use the toes for drawing pictures or working with tools, what would you guess happens to the brain's representation of the toes? Brain scans of two such people found that the brain area devoted to toes did not expand, but it became more specific. Most people's sensory cortex does not distinguish clearly between one toe and another, but the cortex does distinguish between them in people who were forced to use their toes like fingers (Dempsey et al., 2019).

Stop & Check

25. Name two kinds of evidence indicating that touch information from the fingers activates the occipital cortex of people blind since birth.

See page 133 for the answer.

Effects of Music Training

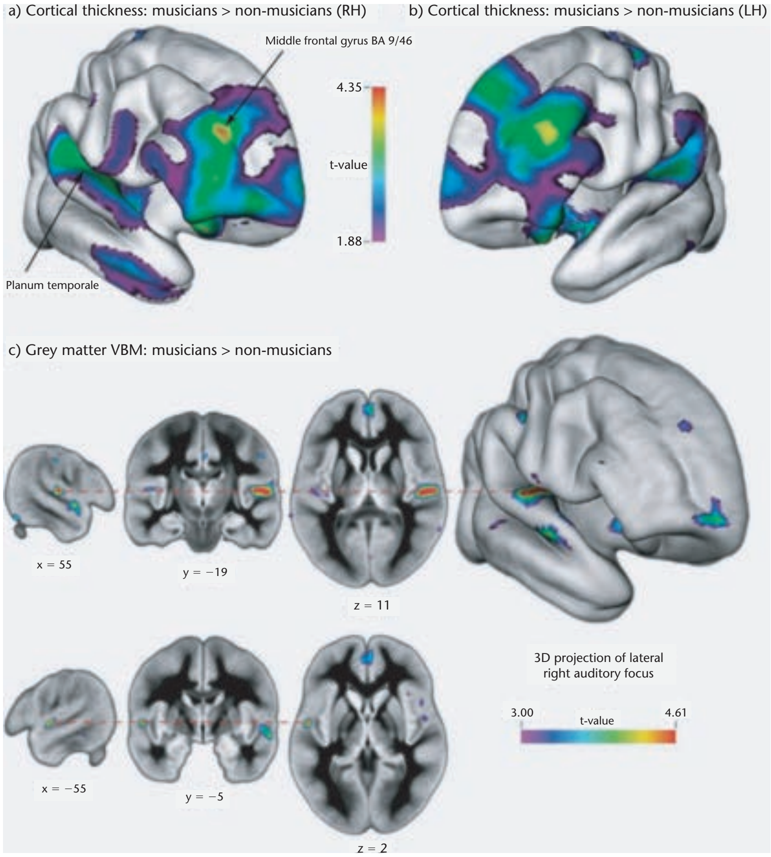
People who develop expertise in any area spend enormous amounts of time practicing, generally beginning in childhood, and it seems reasonable to look for corresponding changes in their brains. Of the various kinds of expertise, researchers' favorite choice has been musicians, for two reasons. First, we have a good idea of where in the brain to look for changes—the brain areas responsible for hearing, finger control, and possibly vision (because it is important for reading music). Second, serious musicians are numerous and easy to find. Almost any big city has an orchestra, and so do most colleges.

The brains of expert musicians differ from those of non-musicians in many ways, including connections between the auditory cortex and other brain areas (Leipold et al., 2021). Two studies found that musicians have greater cortical thickness in several cortical areas than nonmusicians have, as in Figure 4.19 (Bermudez et al., 2009; Gaser and Schlanug, 2003). A related study on stringed instrument players found that a larger than average section of the somatosensory cortex in the right hemisphere was devoted to representing the fingers of the left hand, which they use to control the strings (Elbert et al., 1995). The area devoted to the left fingers was largest in those who began their music practice early and therefore also continued for more years.

These results suggest that practicing music reorganizes the brain. However, an alternative hypothesis is that people who were born with certain brain features are more likely than others to become musicians. A longitudinal study addresses that question. Researchers examined 15 6-year-olds who were beginning piano lessons and 16 other children not taking music lessons. At the start of training, brain scans and

Figure 4.19 Brain correlates of music practice

Areas of the temporal and frontal cortex, marked in blue and green, were thicker in musicians than in nonmusicians. These areas relate to auditory processing and working memory.


a) Cortical thickness: musicians > non-musicians (RH)
b) Cortical thickness: musicians > non-musicians (LH)
Middle frontal gyrus BA 9/46
4.35
t-value
1.88
Planum temporale
c) Grey matter VBM: musicians > non-musicians
x = 55
y = −19
z = 11
x = −55
y = −5
z = 2
3D projection of lateral right auditory focus
3.00
t-value
4.61

(**Source:** Bermudez, P., Lerch, J.P., Evans, A.C., and Zatorre, R.J. (2009). Neuroanatomical correlates of musicianship as revealed by cortical thickness and voxel-based morphometry. Cerebral Cortex 19, pp. 1583–1596.)

cognitive tests showed no significant difference between the groups. After 15 months, the trained group performed better on measures of rhythm and melody discrimination, and they showed enlargements of brain areas responsible for hearing and hand movements, similar to those seen in adult musicians (Hyde et al., 2009a, 2009b). These results imply that at least some of the brain differences are a result of musical training. Another longitudinal study comparing musically trained and untrained children found that the training altered the anatomy of the temporal cortex (Habibi et al., 2020). In still another study, three years of musical training in childhood produced a measurable increase in brainstem responses to sounds (Skoe and Kraus, 2012). However, it is also true that genetic differences predispose some people to better hearing (Palomar-Garcia et al., 2020). In short, both genetics and experience contribute to differences in hearing.

Note that expansion of one brain area after training does not imply that the brain has grown larger. Commonly, as one brain area expands, one or more others contract (Penhune, 2020).

Does music training produce bigger effects if it begins early in life? Several studies found major differences between young adults who started music training in childhood and those who began as teenagers. However, because the adults who started in childhood had practiced for more years, those studies did not separate the effects of starting early from the effects of total years of practice. Two later studies compared people who started music training before age 7 with people who started later but continued for just as many years. In both studies, those who started younger showed greater changes in sensory discriminations and brain anatomy (Steele et al., 2013; Watanabe et al., 2007). A confounding factor is that musicians who started earlier came from families that could afford to provide extra support (Wesseldijk et al., 2021).

Stop & Check

26. Why would the somatosensory cortex of stringed-instrument players show changes in the right hemisphere and not in the left hemisphere?

See page 134 for the answer.

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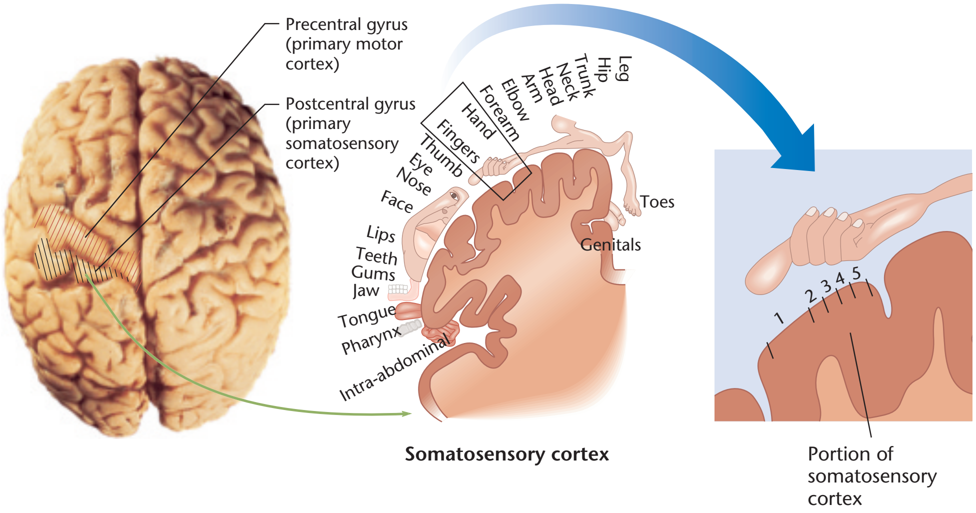
Brain Changes after Briefer Practice

Being blind or deaf from birth leads to altered brain anatomy, and so does long-term musical training. Might briefer experiences also modify brain anatomy? The answer is, "Yes, of course." Even reading this sentence is rearranging a few molecules in your brain. The more interesting question is whether a brief experience produces a big enough effect to be visible with MRI or similar technology.

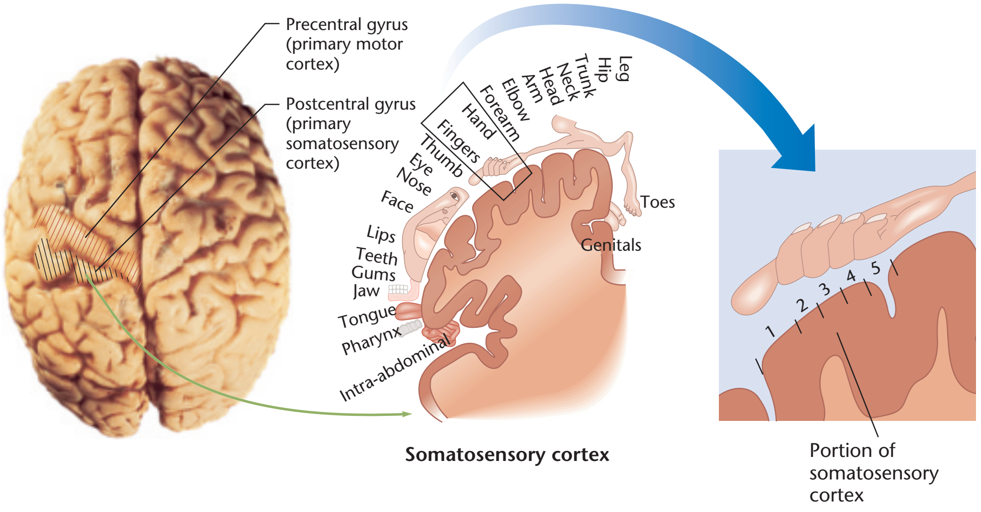
Many studies have in fact reported changes in adult brain anatomy from tasks such as learning to juggle three balls (Draganski et al., 2004; Zatorre et al., 2012), 16 hours of playing a complex video game (Colom et al., 2012), 40 hours of playing golf for the first time (Bezzola et al., 2011), 4 weeks of writing with the nonpreferred hand (Wenger et al., 2017) or 10 weeks of studying a foreign language (Bellander et al., 2016). Skeptics have raised objections (Thomas and Baker, 2013): Many of the studies compared MRIs of the entire brains of the trained group to the entire brains of a control group. In effect, they tested a huge number of hypotheses at once—one hypothesis for each brain area. That procedure has a high risk of finding an apparent result by accident, and we should withhold judgment pending replications. Also, fMRI results depend on the details of testing. If researchers are not careful to test under the same conditions, at the same time of day, they can get spurious results (Steel et al., 2019). One of the most convincing studies found that two brain areas enlarged after briefly learning to juggle three balls and were also expanded (only more so) in expert jugglers (Gerber et al., 2014). The evidence for visible brain changes after extensive practice is reasonably strong (Camels, 2020), but the evidence after brief practice leaves room for doubt.

When Brain Reorganization Goes Too Far

If playing music or practicing anything else expands a relevant brain area, the change is good, right? Usually it is, but not always. As mentioned, when people play musical instruments many hours a day for years, the representation of the hand increases in the somatosensory cortex. Imagine the normal representation of the fingers in the cortex:


Precentral gyrus (primary motor cortex)
Postcentral gyrus (primary somatosensory cortex)
Leg
Hip
Trunk
Neck
Head
Arm
Elbow
Forearm
Hand
Fingers
Thumb
Eye
Nose
Face
Lips
Teeth
Gums
Jaw
Tongue
Pharynx
Intra-abdominal
Toes
Genitals
1
2
3
4
5
Somatosensory cortex
Portion of somatosensory cortex

With extensive musical practice, the expanding representations of the fingers might spread out like this:


Precentral gyrus (primary motor cortex)
Postcentral gyrus (primary somatosensory cortex)
Leg
Hip
Trunk
Neck
Head
Arm
Elbow
Forearm
Hand
Fingers
Thumb
Eye
Nose
Face
Lips
Teeth
Gums
Jaw
Tongue
Pharynx
Intra-abdominal
Toes
Genitals
1
2
3
4
5
Somatosensory cortex
Portion of somatosensory cortex

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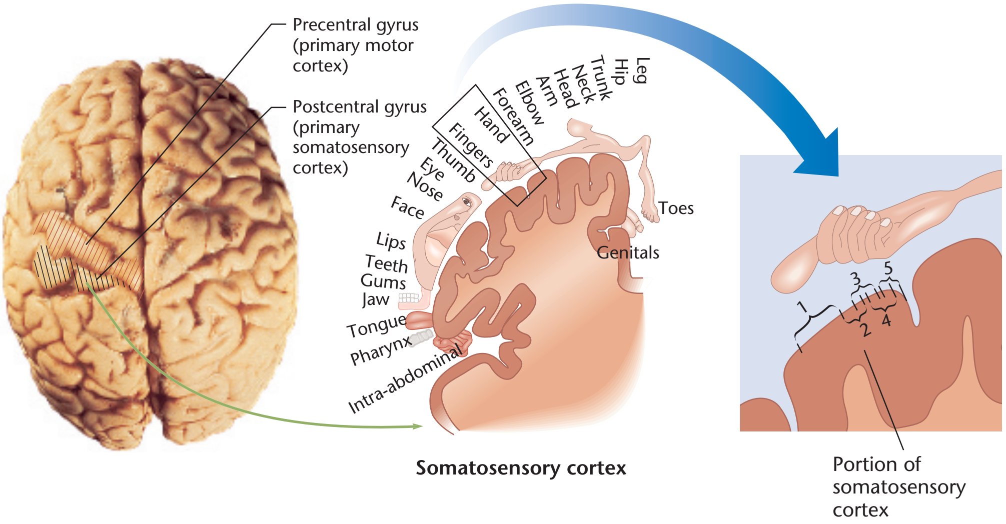
Or the representations of all fingers could grow from side to side without spreading out so that representation of each finger overlaps that of its neighbor:


Precentral gyrus (primary motor cortex)
Postcentral gyrus (primary somatosensory cortex)
Leg
Hip
Trunk
Neck
Head
Arm
Elbow
Forearm
Hand
Fingers
Thumb
Eye
Nose
Face
Lips
Teeth
Gums
Jaw
Tongue
Pharynx
Intra-abdominal
Toes
Genitals
Somatosensory cortex
1
2
3
4
5
Portion of somatosensory cortex

The latter process sometimes occurs after extensive practice, such that the cortical representation of one finger overlaps the representation of another finger (Byl et al., 2000; Elbert et al., 1998; Lenz and Byl, 1999; Sanger et al., 2001; Sanger et al., 2001). If you cannot clearly feel the difference between one finger and another, it might become more difficult to move them independently. Furthermore, the motor cortex might change also. Representation of the middle fingers could expand, overlapping and displacing representation of the index finger and little finger. As a result, one or more fingers may go into constant contraction (Beck et al., 2008; Burman et al., 2009). Moving one finger without moving another becomes more difficult. This condition, known as "musician's cramp" or more formally as **focal hand dystonia**, threatens a musician's career. It is not an automatic consequence of extended practice. It occurs in 1 or 2 percent of professional musicians, based on a combination of extensive practice, anxiety, and a genetic predisposition (Borngraeber and Schmidt, 2020; Latorre et al., 2020).

Previously, physicians assumed that musician's cramp was in the hands themselves, in which case the treatment would be hand surgery or a drug injection into the hand. Now that we have identified brain reorganization as the problem, the approach is to find an appropriate type of retraining. Proprioceptive training provides bursts of vibration to affected muscles or trains the person to reach toward targets. This procedure improves sensation and muscle control for people with musician's cramp and related disabilities (Aman et al., 2015; Rosenkranz et al., 2009). Sometimes wearing latex gloves helps, by

tomas del amo/Alamy Stock Photo

Someone with musician's cramp or writer's cramp has difficulty moving one finger independently of others. One or more fingers may twitch or go into a constant contraction.

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increasing the separation between fingers (Borngraeber and Schmidt, 2020).

Stop & Check

27. What change in the brain is responsible for musician's cramp?

See page 134 for the answer.

Brain Development and Behavioral Development

As people grow older, their behavior changes. Let's consider adolescence and old age.

Adolescence

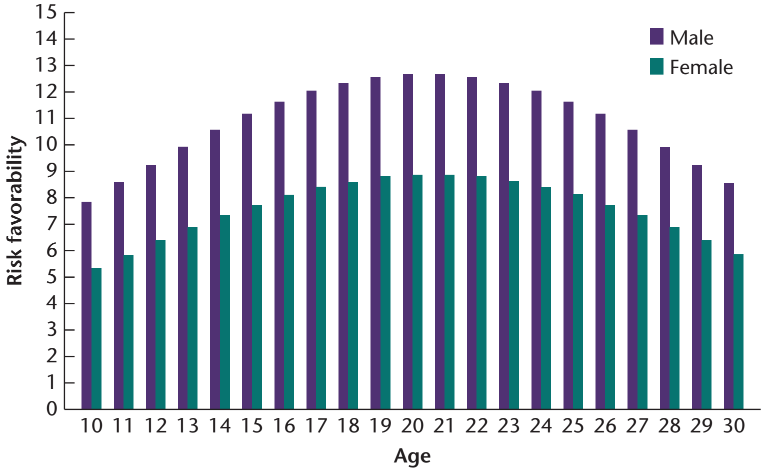
Adolescents are widely regarded as impulsive and prone to seek immediate pleasure, as compared to adults. Impulsiveness is a problem if it leads to risky driving, drinking, sex, spending sprees, and so forth.

In addition to being more impulsive than older adults, children and adolescents tend to "discount the future" more than adults do. Which would you prefer, $100 now or $125 a year from now? What about $100 now versus $150 a year from now? Adolescents are more likely to choose the immediate reward than adults are (Steinberg et al., 2009). To be fair, the situation is not the same for people of different ages, because adults are more likely to be financially secure and better able to wait for a higher reward. Still, adolescents tend to prefer immediate rewards even with other types of reward, and adolescent rats and mice show a similar tendency to prefer immediate food instead of a larger portion later (Doremus-Fitzwater et al., 2012; Pinkston and Lamb, 2011).

Many studies have found that the areas of the prefrontal cortex responsible for inhibiting behaviors are not fully mature in adolescents (e.g., Geier et al., 2010). That type of evidence influenced the U.S. Supreme Court to rule that the death penalty is unconstitutional for adolescents, because adolescents are less able to restrain their impulses (Steinberg, 2013). However, although the prefrontal cortex is indeed not quite mature in adolescents, its immaturity is only a small part of the explanation for impulsivity. In laboratory tests most adolescents inhibit impulses just as well as adults. Most of the riskiest behaviors, especially antisocial risky behaviors, come from individuals with a lifelong history of troublesome behaviors, beginning in childhood and extending into adulthood (Bjork and Pardini, 2015). Furthermore, if risky, impulsive behavior were the product of an immature prefrontal cortex, we should expect it to decline over the teenage years as the cortex gradually matures. Instead, most types of risky behavior become *more* common toward the later teenage years (Figure 4.20) (Shulman, 2014). A likely explanation for risky adolescent behaviors is that the brain's response to rewards, especially anticipation of rewards, increases during the teenage years (Braams et al., 2015; Larsen and Luna, 2015). Adolescents seek excitement, especially when they are trying to impress their peers (Casey and Caudle, 2013; Crone and Dahl, 2012; Luna et al., 2010). From an evolutionary standpoint, we can imagine a possible reason for risky adolescent behaviors. During adolescence and young adulthood, people need to

Figure 4.20 Changes in Attitudes toward Risky Behaviors

People of various ages were asked how favorable they felt toward risky actions such as bicycling down a staircase or surfing in very high waves.



(**Source:** Shulman and Cauffman, 2014)

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find mates and compete for success and prosperity. Doing so requires taking some risks.

Stop & Check

28. Why is immaturity of the prefrontal cortex not a satisfactory explanation for risky behaviors in adolescents?

See page 134 for the answer.

Old Age

On average, old people's memory and reasoning begin to fade. Many neurons lose some of their synapses, and the remaining synapses change more slowly than before in response to experiences (Morrison and Baxter, 2012). The thickness of the temporal cortex shrinks by about half a percent per year, on average (Fjell et al., 2009). The volume of the hippocampus also gradually declines, and certain aspects of memory decline in proportion to the loss of hippocampus (Erickson et al., 2010). Injury or illness causes more rapid than usual decline (Barrientos et al., 2011).

Nevertheless, most chief executives of major corporations, world political leaders, and college presidents are over 60 years old. Some of your professors, too. Is this a problem? Should we fire them and replace them with 25-year-olds? The key phrase in the paragraph above was "on average." Even when researchers limit their study to old people who are healthy without signs of dementia, they inadvertently include people who are in the early stages of dementia, not yet enough to be clearly noticeable. A longitudinal study of adults over age 65 considered separately the results for those who did or did not have elevated levels of chemical markers associated with Alzheimer's disease. The people with those markers showed significantly greater memory declines over time (Harrington et al., 2021).

One factor that increases the chance of retaining strong intellect in old age is a genetic predisposition (Barzilai et al., 2006). Another contributor is consistent physical activity (Fletcher et al., 2016). Experiments that randomly assigned people to daily exercise or sedentary activities show that exercise enhances cortical activity and memory (Muinos and Ballesteros, 2018). Most studies have used consistent moderate exercise, but brief intense activity can be useful also (Moreau and Chou, 2019). Exercise produces its benefits by producing chemicals that stimulate the brain. At least in mice, getting a blood transfusion from either a young mouse or an old mouse that had been exercising increases dendritic branching and improves memory (Horowitz et al., 2020; Villeda et al., 2014). So, if you need to receive a blood transfusion, hope that your donor has been exercising.

Stop & Check

29. Why are reports of declining intellect in old age somewhat misleading?

See page 134 for the answer.

Module 4.2 | In Closing

Brain Development

Once a machine is built, it might need repair, but the construction is finished. Your brain isn't like that. Although the changes are most rapid at first, structural changes continue throughout life. You are forever a work in progress.

Summary

1. In vertebrate embryos, the central nervous system begins as a tube surrounding a fluid-filled cavity. Developing neurons proliferate, migrate, differentiate, and develop synapses and myelin. Neuron proliferation varies among species mainly by the number of cell divisions. Migration depends on chemicals that guide immature neurons to their destinations. **117**
2. Adult vertebrates replace dying olfactory receptors with new ones, and they form new neurons only in a few parts of the brain, including the hippocampus. In adult humans it is uncertain or doubtful that new neurons form in the hippocampus. **119**
3. Growing axons find their way close to the right locations and then arrange themselves over a target area by following chemical gradients. **120**
4. After axons reach their targets based on chemical gradients, the postsynaptic cell adjusts the connections based on experience, accepting certain combinations of axons and rejecting others. This kind of competition among axons continues throughout life. **122**

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5. Initially, the nervous system develops more neurons than will survive. Axons of the sympathetic nervous system survive only if they reach a target cell that releases nerve growth factor to them. Otherwise, they die in a process called apoptosis. As the brain matures, it loses neurons, especially those not receiving sufficient excitation. **122**

6. The developing brain is vulnerable to chemical insult. Many chemicals that produce only mild, temporary problems for adults can impair early brain development. **123**

7. At an early stage of development, the cortex is sufficiently plastic that visual input can cause what would have been the auditory cortex to develop different properties and now respond visually. **124**

8. Enriched experience leads to greater branching of axons and dendrites, partly because animals in enriched environments are more active than those in deprived environments. **125**

9. Specialized experiences can alter brain development. For example, the representation of fingers expands in people who regularly practice musical instruments. **127**

10. Although expanded representation in the brain is ordinarily a good thing, it can be harmful if carried too far. Some musicians and others who use their hands many hours each day develop brain changes that interfere with their ability to feel or use one finger independently of the others. **129**

11. Compared to adults, adolescents tend to be impulsive and centered more on present pleasures than on future prospects. Risky behaviors in adolescents probably reflects increased drive for excitement, more than lack of ability to inhibit impulses. **131**

12. On average, people in old age show declining memory and reasoning, and shrinkage of certain brain areas. However, the averages do not apply to all individuals or all situations. Physically active people tend to maintain their cognitive abilities. **132**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

apoptosis	**122**
differentiates	**118**
far transfer	**126**
fetal alcohol syndrome	**124**
focal hand dystonia	**130**
migrate	**118**
myelination	**119**
nerve growth factor (NGF)	**122**
neural darwinism	**122**
neurotrophin	**123**
proliferation	**118**
stem cells	**118**
synaptogenesis	**118**

Thought Question

1. What would happen if someone injected antibodies against nerve growth factor into a developing nervous system?

Stop & Check Answers

13. Spontaneous activity in the spinal cord.

14. Migration occurs first.

15. Olfaction

16. The mean ^{14}C concentration in the DNA of cortical neurons corresponds to the year of birth.

17. If he cut connections to a newt's eye and inverted the eye, axons grew back to their original targets, even though the connections were inappropriate to their new positions on the eye.

18. The axons would attach based on a chemical gradient but could not fine-tune their adjustment based on experience. Therefore, the connections would be less precise.

19. The nervous system builds more neurons than it needs and discards through apoptosis those that do not make lasting synapses.

20. Neurotrophins, such as nerve growth factor

21. The neuron number is greatest during early development.

22. Increased GABA activity decreases excitation, and developing neurons undergo apoptosis if they do not receive enough excitation.

23. They trained the ferrets to respond to stimuli on the normal side, turning one direction in response to sounds and the other direction to lights. Then they presented light to the rewired side and saw that the ferret again turned in the direction it had associated with lights.

24. Animals in an enriched environment are more active, and their exercise enhances growth of axons and dendrites.

25. First, brain scans indicate increased activity in the occipital cortex while blind people perform tasks such as feeling two objects and saying whether they are the same or different. Second, temporary inactivation of the occipital cortex impairs blind people's ability to perform that task, without affecting the ability of sighted people.

26. Stringed-instrument players finger the strings only with the left hand, which the right hemisphere controls.

27. Extensive practice of an instrument causes expanded representation of the fingers in the somatosensory cortex, as well as modified representation of one or more fingers in the motor cortex. If the representation of two fingers overlaps too much, the person cannot feel them separately or move them separately.

28. As the teenage years progress, risky behavior tends to increase, even while the prefrontal cortex is becoming more mature.

29. The reports present averages, but the average performance is depressed by people who are in the early stages of Alzheimer's disease or other disorders.

Module 4.2 | End-of-Module Quiz

1. In early human brain development, which of these develops first?

a. Vision
b. Hearing
c. Muscle movements
d. Sense of touch

2. How long does myelination continue in humans?

a. During the second trimester of pregnancy
a. Until shortly after birth
b. Until adolescence
c. For decades

3. In which sensory system do new receptors continue to form throughout life?

a. Olfaction
b. Vision
c. Hearing
d. Pain

4. What evidence demonstrated that new neurons do not form in the adult human cortex?

a. Counts of the number of neurons sometimes go down, but never up.
b. The glia-to-neuron ratio increases throughout life.
c. The ^{14}C concentration of cortical cells is characteristic of the year of birth.
d. Cortical neurons gradually change color as they grow older.

5. When Roger Sperry cut a newt's optic nerve and turned the eye upside down, what happened?

a. Axons of the optic nerve grew randomly and attached diffusely to target cells.
b. Axons of the optic nerve grew back to their original targets.
c. Axons of the optic nerve grew back to targets appropriate to their new location in the eye.
d. At first the axons grew back randomly, but then they established appropriate connections by learning.

6. What did Rita Levi-Montalcini discover?

a. An enriched environment increases the growth of axons and dendrites.
b. Axons distribute themselves over a surface by following a gradient of chemicals.
c. Exposure to alcohol during early development kills many neurons.
d. Sympathetic nervous system axons die if they do not connect to a muscle.

7. At what age does a person have the largest number of neurons?

a. Before or shortly after birth
b. Equally at all times of life
c. Adolescence
d. Adulthood

8. What does apoptosis cause?

a. A balance between excitatory and inhibitory synapses
b. Increased velocity of action potentials
c. The correct ratio of neurons to glia cells
d. The removal of ineffective neurons

9. In the ferret study, what evidence indicated that visual input to the auditory portions of the brain produced a visual sensation?

a. Bright flashes of light to the rewired eye caused the ferrets to blink both eyes.
b. Recordings from individual cells of the rewired temporal cortex showed the same patterns usually seen in cells of the occipital cortex.
c. Ferrets could find their way around an unfamiliar room even with the normal eye closed.
d. Ferrets that learned to turn one way in response to light in the normal eye turned the same way to light in the rewired eye.

10. An enriched environment including social interactions promotes growth of axons and dendrites in laboratory rodents. What else can produce the same effect?

a. Improved diet
b. Physical activity
c. Exposure to music
d. Extra sleep

11. On what part(s) of the body, if any, do blind people have greater than average touch sensitivity?

a. All of the body
b. The face
c. The fingers
d. No part of the body

12. In people who practice violin or other stringed instruments for many years, what changes in the cerebral cortex?

- **a.** Both hemispheres begin controlling speech equally.
- **b.** Parts of the occipital cortex stop responding to vision and switch to hearing.
- **c.** A larger than average portion of the cortex responds to the passage of time.
- **d.** A larger than average portion of the cortex responds to fingers of the left hand.

13. What causes focal hand dystonia (musician's cramp)?

- **a.** Changes in the muscles and tendons of the hand
- **b.** Rewiring of the cerebral cortex
- **c.** Loss of myelin on the motor nerves to the hand
- **d.** Changes in the touch receptors of the hand

14. What is the most likely biological explanation for increased risky behavior among adolescents?

- **a.** Immaturity of the prefrontal cortex
- **b.** Increased activity in brain areas that anticipate reward
- **c.** Increased activity in brain areas responsible for depressed mood
- **d.** Immaturity of the corpus callosum

Answers: 1c, 2d, 3a, 4c, 5b, 6d, 7a, 8d, 9d, 10b, 11c, 12d, 13b, 14b.

Module 4.3

Plasticity after Brain Damage

Learning Objectives

After studying this module, you should be able to:

14. List possible mechanisms of recovery after brain damage.

15. Explain how remodeling in the cerebral cortex produces the phantom limb experience.

An American soldier who suffered a wound to the left hemisphere of his brain during the Korean War was at first unable to speak at all. Three months later, he could speak in short fragments. When he was asked to read the letterhead, "New York University College of Medicine," he replied, "Doctors—little doctors." Eight years later, when someone asked him again to read the letterhead, he replied, "Is there a catch? It says, 'New York University College of Medicine'" (Eidelberg and Stein, 1974).

Almost all survivors of brain damage show behavioral recovery to some degree. The brain always shows plasticity, but after damage, it is forced to make more drastic adjustments.

Brain Damage and Immediate Treatments

Possible causes of brain damage include tumors, infections, exposure to radiation or toxic substances, and degenerative conditions such as Parkinson's disease and Alzheimer's disease. In young people, the most common cause is **closed head injury**, a sharp blow to the head that does not puncture the brain. The effects of closed head injury depend on severity and frequency. Most children and young adults sustain at least one mild blow to the head from a fall, a bicycle or automobile accident, or a sports injury. Most recover without treatment (Babikian et al., 2015). However, about 7 or 8 young people per thousand require hospital treatment, and of those, about 20 percent suffer a persisting disability (Thurman, 2016). Some seem to recover but develop additional problems later (Holden et al., 2021). The risk is greater after repeated blows to the head, which are common for people playing contact sports such as rugby or football (Van Pelt et al., 2021).

One cause of damage after closed head injury is the rotational forces that drive brain tissue against the inside of the skull. Another cause is blood clots that interrupt blood flow to the brain (Kirkpatrick et al., 1995). Given the dangers from a blow to the head, how do woodpeckers manage to avoid giving themselves concussions? If you banged your head into a tree 20 times per second at a speed strong enough to tear a hole in the bark, you would not be in good shape.

Using slow-motion photography, researchers found that woodpeckers usually start with a couple of quick preliminary taps against the wood, like a carpenter lining up a nail with a hammer. Then the birds make a hard strike in a straight line, keeping a rigid neck. They almost completely avoid rotational forces and whiplash (May et al., 1979). Furthermore, the spongy bone of the woodpecker's head makes an excellent shock absorber (Yoon and Park, 2011).

The implication is that football helmets, race car helmets, and so forth would give more protection if they extended down to the shoulders to prevent rotation and whiplash. If you think you are about to be in a crash, tuck your chin to your chest and tighten your neck muscles.

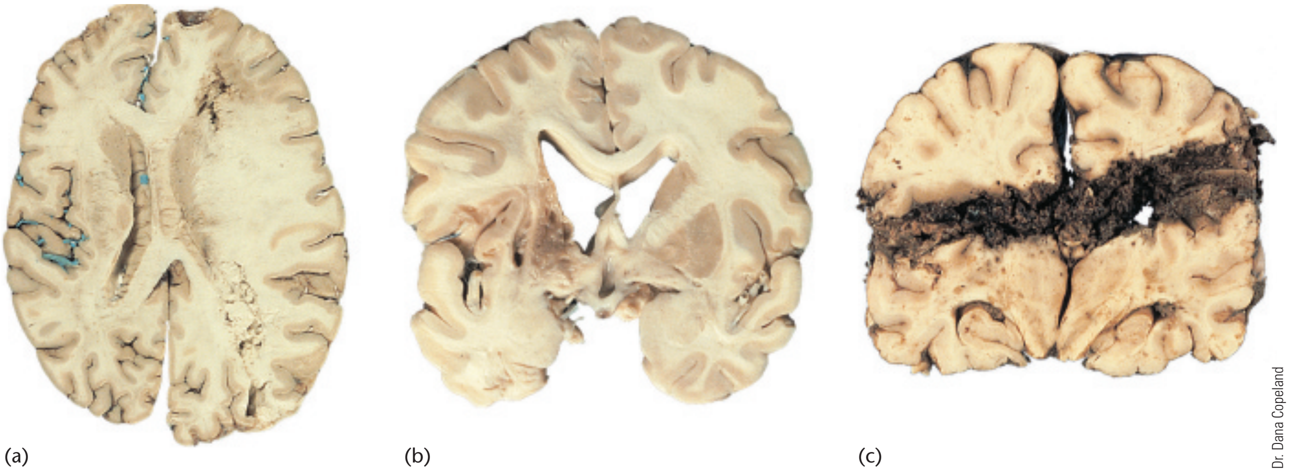
A common cause of brain damage, especially in older people, is temporary interruption of normal blood flow to a brain area during a **stroke**, also known as a **cerebrovascular accident**. The more common type of stroke is **ischemia** (iss-KEE-me-uh), the result of a blood clot or other obstruction in an artery. The less common type is **hemorrhage** (HEM-oh-rage), the result of a ruptured artery. Effects of strokes vary from barely noticeable to immediately fatal. Figure 4.21 shows the brains of three people: one who died immediately after a stroke, one who survived long after a stroke, and a bullet wound victim.

In ischemia, the neurons deprived of blood lose much of their oxygen and glucose supplies. Also, cerebrospinal fluid flows into the brain and rapidly accumulates, causing swelling of the brain that produces widespread damage (Mestre et al., 2020). In hemorrhage, neurons are flooded with blood and excess oxygen, calcium, and other chemicals, again causing **edema** (accumulation of fluid). Both ischemia and hemorrhage also impair the sodium–potassium pump, leading to an accumulation of sodium inside neurons. The combination of edema and excess sodium releases excess glutamate, which overstimulates neurons, causing damage (Castro-Alvarez et al., 2011; Rossi et al., 2000).

Prospects are good for relieving ischemia if physicians act quickly. A drug called **tissue plasminogen activator (tPA)** breaks up blood clots. To get a benefit, a patient

Figure 4.21 Three damaged human brains

(a) Brain of a person who died immediately after a stroke. Note the swelling on the right side. (b) Brain of someone who survived for a long time after a stroke. Note the cavities on the left side, where many cells were lost. (c) Brain of a person who suffered a gunshot wound and died immediately.



(**Source:** Courtesy of Dana Copeland)

should receive tPA quickly, preferably within 4.5 hours after a stroke, although some studies suggest benefits at up to 9 hours. Emergency wards and ambulances have improved their response times, but most stroke victims don't get help quickly enough, because neither they nor their family recognize the problem at once.

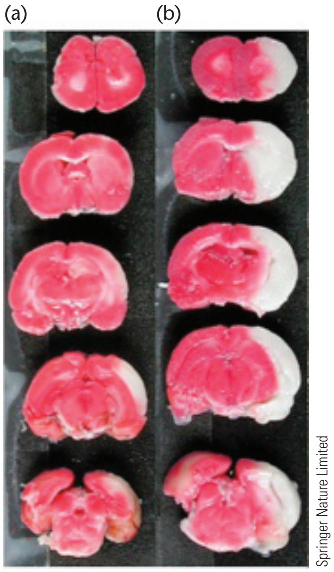
It is difficult to determine whether a stroke was ischemic or hemorrhagic. Given that tPA is useful for ischemia but could only make matters worse in a hemorrhage, what is a physician to do? An MRI scan distinguishes between the two kinds of stroke, but MRIs take time, and time is limited. The usual decision is to give the tPA. Hemorrhage is less common and usually fatal anyway, so the risk of making a hemorrhage worse is small compared to the hope of alleviating ischemia.

What other treatments might be effective shortly after a stroke? Given that strokes kill neurons by overstimulation, one approach has been to use procedures that block glutamate synapses, block calcium entry, or protect neurons in other ways. Although many such procedures have shown promise in laboratory animals, they have had disappointing results in people. Most of the lab studies used animals that were young and healthy before the stroke, whereas most human stroke patients are old and have high blood pressure or other health problems (Candelario-Jalil and Paul, 2021).

Another procedure might surprise you: Exposure to cannabinoids (the chemicals found in marijuana) minimizes the damage caused by strokes in laboratory animals. You might wonder how anyone thought of trying such a thing. One theoretical rationale was that cannabinoids decrease the release of glutamate. If excessive glutamate is one of the reasons for cell loss, then cannabinoids might be helpful. They do, in fact, minimize the damage after a stroke in rats, as shown in Figure 4.22, although blocking glutamate is probably not the reason. Cannabinoids exert anti-inflammatory effects, protect the blood–brain barrier,

Figure 4.22 Effects of a cannabinoid on stroke damage

Row (a) shows slices through the brains of five rats treated with a high dose of a cannabinoid shortly after a stroke. Row (b) shows slices for rats not treated with cannabinoids. The white areas on the right of each brain show the extent of the damage.



(From "Endocannabinoids mediate neuroprotection after transient focal cerebral ischemia," by M. Schomacher, H. D. Müller, C. Sommer, S. Schwab, and W.-R. Schäbitz, 2008, *Brain Research, 1240*, pp. 213–220.)

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reduce edema, and lower body temperature after a stroke (Cristino et al., 2020; Fernández-Ruiz et al., 2015). All those effects contribute to the benefits. The benefits almost certainly come from cannabidiol, the non-intoxicating component of marijuana, and not from THC.

So far, not much research has examined possible effects of cannabidiol for human stroke patients. According to the research with laboratory animals, the drug is helpful only if administered quickly after a stroke, or better yet, shortly *before* the stroke. (I guess if you were expecting to have a stroke…) One study did find that stroke patients with cannabinoids in their bloodstream, indicating marijuana use before the stroke, had on average less severe damage from the stroke (Di Napoli et al., 2016). However, the mean age of the marijuana users in that study was 47, and the mean for nonusers was 69. It is difficult to know how much of the difference in outcome was due to a possibly beneficial effect of marijuana, and how much was related to age.

Stop & Check

30. Why is tPA not helpful in cases of hemorrhage?
31. Why have researchers tried blocking glutamate synapses for stroke patients?

See page 143 for the answer.

Later Mechanisms of Recovery

Ischemia kills a cluster of cells that were starved of blood. Surrounding that cluster is the *penumbra*, a set of cells that are impaired by having less than the usual amount of blood. Axons near the damage are also impaired because of chemicals spreading from the area of damage (Hsu et al., 2021). More distant cells may also be less active because of decreased input from the killed or impaired cells. Nevertheless, during the weeks after a stroke or other damage, neurons show greater than their usual level of plasticity, comparable to the changes in early brain development (Joy and Carmichael, 2021). Let's consider some of the changes that happen spontaneously and some possibilities for medical intervention.

Overcoming Diaschisis

After damage to any brain area, other areas that have lost part of their normal input become less active. For example, shortly after damage in one brain hemisphere, its input to the other hemisphere declines, and therefore the other hemisphere shows deficits also (van Meer et al., 2010).

Diaschisis (di-AS-ki-sis, from a Greek term meaning "to shock throughout") refers to the decreased activity of surviving neurons because of damage to other neurons. When diaschisis contributes to behavioral deficits following brain damage, increased stimulation should help. In a series of experiments, D. M. Feeney and colleagues measured the behavioral effects of cortical damage in rats and cats. Depending on the location of the damage, the animals showed impairments in movement or depth perception. Injecting amphetamine significantly enhanced both behaviors, and animals that practiced the behaviors under the influence of amphetamine showed long-lasting benefits. Injecting a drug to block dopamine synapses impaired behavioral recovery (Feeney and Sutton, 1988; Feeney et al., 1985; Hovda and Feeney, 1989; Sutton et al., 1989).

Regrowth of Axons

Damage to the brain or spinal cord kills cells, and it also cuts axons. Getting the axons to grow back and connect to the correct targets could offer a great benefit. In principle, axon regrowth would seem to be possible. A damaged axon in the peripheral nervous system does grow back at a rate of about 1 mm per day, following its myelin sheath to the original target. Damaged axons also grow back in both the retina and the spinal cord of fish, under the control of chemicals that are absent in adult mammals (Anderson et al., 2018; Jorstad et al., 2017; Mokalled et al., 2016; Zhang et al., 2014). However, axons do not grow back in the adult mammalian brain or spinal cord, at least not enough to produce any benefit. If axons can grow back in fish, why not in mammals?

A cut in the nervous system causes astrocytes to form scar tissue, thicker in mammals than in fish. One hypothesis was that scar tissue is the main impediment, and that reducing the scar tissue might enable axon regrowth. However, later studies indicated that the scar tissue produces a mixture of effects. Astrocytes that form at the scar produce chemicals called *chondroitins* that inhibit axon regeneration, but they also reduce inflammation that would spread the damage. Overall, preventing scar formation is more harmful than helpful (Adams and Gallo, 2018; Anderson et al., 2016; Rosenzweig et al., 2019; Sabelström et al., 2013).

Several chemicals can stimulate axon regrowth, and research with laboratory rats has shown that such chemicals sometimes enable axons to return to their normal targets (Anderson et al., 2016; Ruschel et al., 2015; Wong et al., 2015). Electrical stimulation of receptors in the spinal cord can also help rats regain movement after spinal cord damage (Asboth et al., 2018). In each case, to get proper function, the animal needs to practice the relevant movements (Abe et al., 2018; Hollis et al., 2016; Wahl et al., 2014).

One promising approach uses glial cells derived from a patient's olfactory bulb. Transplanting those cells to spots just above and below the area of damage in a spinal cord produced partial recovery of both sensation and movement in a small number of patients (Tabakow et al., 2014). More research is needed to refine the procedure and to understand exactly how it works.

Stop & Check

32. What procedures have improved recovery in rats with damage to the brain or spinal cord?

See page 143 for the answer.

Axon Sprouting

Ordinarily, the surface of dendrites and cell bodies is covered with synapses, and a vacant spot doesn't stay vacant for long. After a cell loses input from an axon, it secretes neurotrophins that induce other axons to form new branches, or **collateral sprouts**, that take over the vacant synapses (Ramirez, 2001) (Figure 4.23). In the area near the damage, sprouting and new synapses form at a higher than usual rate, especially in the first weeks (Lotze et al., 2019).

Collateral sprouting in the cortex contributes to behavioral recovery in some cases (e.g., Li et al., 2015; Siegel et al., 2015). However, the result depends on whether the sprouting axons convey information similar to that of the axons that they replace. For example, the hippocampus receives much input from an area called the entorhinal cortex. If the entorhinal cortex is damaged in one hemisphere, then axons from the entorhinal cortex of the other hemisphere sprout, take over the vacant synapses, and largely restore behavior (Ramirez et al., 1999; Ramirez et al., 1996). However, if the entorhinal cortex is damaged in both hemispheres, then axons from other locations sprout into the vacant synapses, conveying different information. Under those conditions, the sprouting interferes with behavior and prevents recovery (Ramirez, 2001; Ramirez et al., 2007).

Denervation Supersensitivity

Neurons make adjustments to maintain a nearly constant level of arousal. After learning strengthens one set of synapses, other synapses weaken. (If this didn't happen, then every time you learned something, your brain would get more and more aroused.) Conversely, if a certain set of synapses becomes inactive—perhaps because of damage to incoming axons—the remaining synapses become more responsive, more easily stimulated. This process of enhanced response, known as **denervation supersensitivity** or *receptor supersensitivity*, has been demonstrated mostly with dopamine synapses (Kostrzewa et al., 2008).

Denervation supersensitivity helps compensate for decreased input. However, when either collateral sprouting or denervation supersensitivity occurs, it can strengthen not only the desirable connections but also undesirable ones, sometimes those responsible for pain. Unfortunately, many treatments that facilitate the regrowth of axons in a damaged spinal cord also lead to chronic pain (Brown and Weaver, 2012).

Stop & Check

33. Does collateral sprouting occur in axons or dendritic receptors?
34. Does denervation supersensitivity occur in axons or dendritic receptors?

See page 143 for the answer.

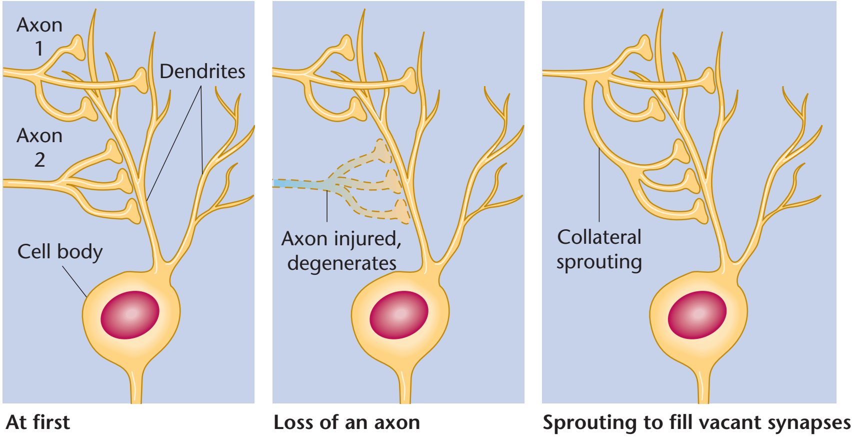
Reorganized Sensory Representations and the Phantom Limb

If a brain area loses some of its incoming axons, we can expect denervation supersensitivity, collateral sprouting, or both. The result is either increased response to a synapse, or response to an axon that previously did not attach at all. Let's imagine how these processes might apply after an amputation.

Reexamine Figure 3.23. Each section of the somatosensory cortex receives input from part of the body. Within the area marked "fingers" in that figure, a closer examination reveals that each subarea responds more to one finger than to others. Figure 4.24 shows the arrangement for a monkey brain. After experimenters amputated finger 3 of an owl monkey, the cortical cells that previously responded

Figure 4.23 Collateral sprouting

A surviving axon grows a new branch to replace the synapses left vacant by a damaged axon.



At first **Loss of an axon** **Sprouting to fill vacant synapses**

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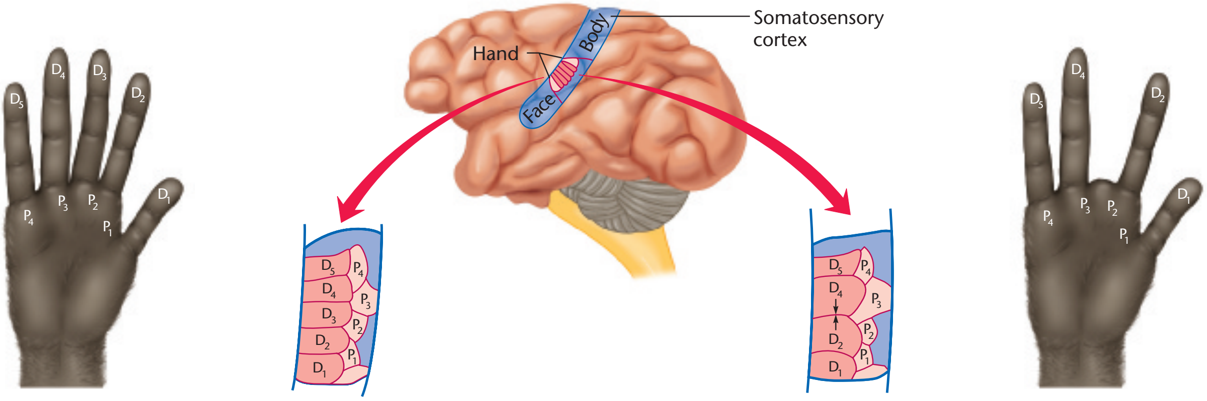
Figure 4.24 Somatosensory cortex of a monkey after a finger amputation

Note that the cortical area previously responsive to the third finger (D_3) becomes responsive to the second and fourth fingers (D_2 and D_4) and part of the palm (P_3).



(a) Normal (before amputation)

(b) After amputation of 3rd digit

(Redrawn from the *Annual Review of Neuroscience*, Vol. 6, © 1983, by Annual Reviews, Inc. Reprinted by permission of Annual Reviews, Inc. and Jon H. Kaas.)

to that finger lost their input. Soon they became more responsive to finger 2, finger 4, or part of the palm, until the cortex developed the pattern of responsiveness shown in Figure 4.24b (Kaas et al., 1983; Merzenich et al., 1984).

What happens if an entire arm is amputated? For many years, neuroscientists assumed that the cortical area corresponding to that arm would remain permanently silent, because axons from other cortical areas could not sprout far enough to reach the area representing the arm. Then came a surprise. Investigators recorded from the cerebral cortices of monkeys whose sensory nerves from one forelimb had been cut 12 years previously. They found that the stretch of cortex previously responsive to that limb was now responsive to the face (Pons et al., 1991). The change had not required 12 years, but the researchers simply had not checked before then.

The loss of sensory input from a monkey's forelimb had left vacant synaptic sites at several levels of the CNS. Evidently, axons representing the face sprouted into those sites in the spinal cord, brainstem, and thalamus (Florence and Kaas, 1995; Jones and Pons, 1998). Or perhaps axons from the face were already present but became stronger through denervation supersensitivity. Brain scan studies confirm that the same processes occur with humans.

Now consider that reorganized cortex. The cells that previously responded to arm stimulation now receive information from the face. Does it feel like touch on the face or on the arm? The answer: It feels like the arm (Davis et al., 1998). Evidently the brain areas that start off as arm areas, hand areas, or whatever retain those properties even after decades without normal input. One patient had a hand amputated at age 19; 35 years later, a new hand was grafted in its place. Within months, he started to feel normal sensations in that hand (Frey et al., 2008).

Physicians have long noted that many people with amputations experience a **phantom limb**, a continuing sensation of an amputated body part. That experience can range from tingling to intense pain, either occasionally or constantly (Giummarra et al., 2010). People can have a phantom hand, foot, or any other body part. The phantom sensation might last days, weeks, or a lifetime (Ramachandran and Hirstein, 1998).

David Shankbone/
Wikimedia Commons

V. S. Ramachandran

The overall strategy is to investigate neurological dysfunction … and ask: Why does this patient display these curious symptoms? What do the symptoms tell us about the workings of the normal brain? Can a careful study of these patients help us explain how the activity of a hundred billion nerve cells in the brain give rise to all the richness of our conscious experience? (Ramachandran, 2004, p. ix)

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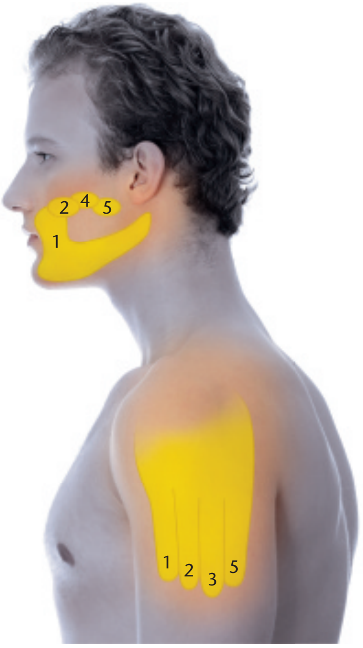
Until the 1990s, no one knew what caused phantom pains, and most physicians believed that the sensations came from the stump of the amputated limb. However, removing more of the limb in an attempt to eliminate the phantom sensations accomplished nothing. Modern methods show that phantom limbs develop when the relevant portion of the somatosensory cortex reorganizes and becomes responsive to alternative inputs (Flor et al., 1995). For example, suppose axons representing the face come to activate the cortical area previously devoted to an amputated hand. A touch on the face now produces a facial sensation but it also produces a phantom hand sensation. Figure 4.25 shows a map of which face area stimulated sensation in which part of the phantom hand, for one person (Aglioti et al., 1997). For some people, seeing someone else being touched can also elicit a sensation in the phantom limb (Goller et al., 2013).

Note in Figure 3.23 that the part of the cortex responsive to the feet is adjacent to the part responsive to the genitals. Two patients with foot amputations felt a phantom foot during sexual arousal! One reported feeling orgasm in the phantom foot as well as the genitals—and enjoyed it intensely (Ramachandran and Blakeslee, 1998). Evidently, the representation of the genitals had spread into the cortical area responsible for foot sensation.

Figure 4.25 Sources of phantom sensation for one person

Stimulation in the areas marked on the cheek produced phantom sensations of digits 1 (thumb), 2, 4, and 5. Stimulation on the shoulder also evoked phantom sensations of digits 1, 2, 3, and 5.



(Figure 5.29 from *Phantoms in the Brain* by V. S. Ramachandran, M.D., Ph.D. and Sandra Blakeslee. Copyright © 1998 by V. S. Ramachandran and Sandra Blakeslee. Reprinted by permission of HarperCollins Publishers and authors.)

AP Images/Andy Manis

Amputees who feel a phantom limb are likely to lose those phantom sensations if they learn to use an artificial arm or leg.

Is there any way to relieve a painful phantom sensation? In some cases, yes. Many amputees who learn to use an artificial arm report that their phantom sensations gradually disappear (Lotze et al., 1999). As they start attributing sensations to the artificial arm, they suppress the connections that caused phantom sensations.

Stop & Check

35. What is responsible for the phantom limb experience?

See page 143 for the answer.

Learned Adjustments in Behavior

If you cannot find your keys, perhaps you accidentally dropped them into the trash (so they are gone forever), or perhaps you absentmindedly put them in an unusual place (where you will find them if you keep looking). Similarly, someone with brain damage may have lost an ability, or may be able to find it with enough effort. Much recovery from brain damage depends on learning to make better use of

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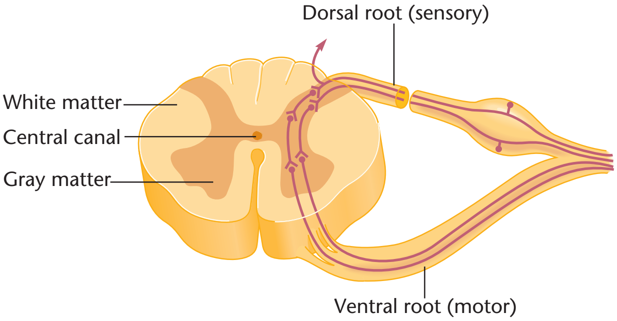
the abilities that were spared. For example, if you lose your peripheral vision, you could move your head from side to side to compensate (Marshall, 1985). If you lose control of your fingers, you might move your arm and trunk to guide the fingers to a desired place. If you have trouble moving a leg, you might amplify the leg movement by exaggerated arm movements (Jones, 2017).

Often, a person or animal with brain damage who appears unable to do something is just not trying. Consider an animal that incurred damage to the sensory nerves from a forelimb to the spinal cord, as in Figure 4.26. The animal no longer feels the limb, but the motor nerves still connect to the muscles. We say the limb is **deafferented** because it lost its afferent (sensory) input. A monkey with a deafferented limb does not use it for walking, picking up objects, or any other voluntary behaviors (Taub and Berman, 1968). At first investigators assumed that the monkey was unable to use the deafferented limb. In a later experiment, however, they cut the afferent nerves of both forelimbs. After this more extensive damage, the monkey used both of the deafferented limbs to walk, climb, and pick up food. Apparently, a monkey fails to use one deafferented forelimb only because walking on three limbs is easier than using an impaired limb. When it has no choice but to use its deafferented limbs, it does. Similarly, one treatment for people recovering from a stroke is to force them to use the weaker limb by preventing them from using the normal limb (Sens et al., 2012).

Figure 4.26 Cross section through the spinal cord

A cut through the dorsal root (as shown) deprives the animal of touch sensations from part of the body but leaves the motor nerves intact.



Therapy for someone with brain damage begins with careful evaluation of a patient's abilities and disabilities. For example, if someone has trouble following spoken instructions, what is the problem? It might be impaired hearing, memory, language, muscle control, or alertness. After identifying the problem, a physical therapist or occupational therapist helps the patient practice the impaired skills. Training is most effective during the first few months after damage (Lotze et al., 2019).

Behavior recovered after brain damage is effortful, and its recovery is precarious. A person with brain damage who appears to be functioning normally is working harder than usual. The recovered behavior deteriorates markedly after drinking alcohol, physical exhaustion, or other kinds of stress that would minimally affect most other people (Fleet and Heilman, 1986). It also deteriorates in old age (Corkin et al., 1989).

Stop & Check

36. A monkey that loses sensation from one arm stops using it, but a monkey that loses sensation from both arms does use them. Why?

See page 143 for the answer.

Module 4.3 | In Closing

Brain Damage and Recovery

Let's imagine a company that is like a human brain. One important person retires. Because this company is like a brain, it can't hire a replacement, because that would be like growing a new neuron. Temporarily, the company fares badly, because it misses that person's work, and many other people in the company lack the input they need to do their jobs. Within days or weeks, the company finds a way for other people to do some of the work of the retired person. The company might not operate quite as well as before, but it does what it can. Recovery from brain damage is like that.

Summary

1. Brain damage has many causes, including blows to the head, obstruction of blood flow to the brain, or a ruptured blood vessel in the brain. Strokes kill neurons largely by overexcitation. **136**
2. During the first hours after an ischemic stroke, tissue plasminogen activator (tPA) can reduce cell loss by breaking up the blood clot. **136**
3. Many procedures for reducing the effects of nervous system injury have shown promise with laboratory animals,

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but so far none of them have been reliably helpful with humans. **137**

4. When one brain area is damaged, other areas become less active than usual because of their loss of input. Stimulant drugs can help restore normal function of these undamaged areas. **138**
5. After an area of the CNS loses its usual input, other axons begin to excite it by either collateral sprouting or denervation supersensitivity. The anatomical reorganization is helpful in some cases but not always. **139**
6. The phantom limb experience occurs because axons from another body part activate the cortical area ordinarily devoted to sensation from the lost body part. Stimulation of the other body part now produces sensation as if it had come from the amputated part. **139**
7. Much recovery after brain damage results from learning to make better use of the abilities that were spared. **141**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

cerebrovascular accident	**136**
closed head injury	**136**
collateral sprouts	**139**
deafferent	**142**
denervation supersensitivity	**139**
diaschisis	**138**
edema	**136**
hemorrhage	**136**
ischemia	**136**
phantom limb	**140**
stroke	**136**
tissue plasminogen activator (tPA)	**136**

Thought Questions

1. Ordinarily, patients with advanced Parkinson's disease (with damage to dopamine-releasing axons) move slowly if at all. However, during an emergency (e.g., a fire in the building), they may move rapidly and vigorously. Suggest a possible explanation.
2. Drugs that block dopamine synapses (such as some that are prescribed for schizophrenia) tend to impair or slow limb movements. However, some people who have taken such drugs for a long time experience involuntary muscle twitches or tremors. Based on material in this chapter, propose a possible explanation.

Stop & Check Answers

30. The drug tPA breaks up blood clots, and hemorrhage results from a ruptured blood vessel, not a blood clot.
31. Stokes kill many neurons by overstimulation, which depends on glutamate.
32. Amphetamine stimulates cells that are impaired by decreased input from the damaged area. Chemicals that stimulate axon growth can help, and so can electrical stimulation. In each case, the improvement requires practice of the relevant behaviors.
33. Axons
34. Dendritic receptors
35. Synapses that used to receive input from the now amputated part become vacant. Axons representing another part of the body take over those synapses. Now stimulation of this other part activates the synapses associated with the amputated area, but that stimulation feels like the amputated area.
36. A monkey that lost sensation in one arm is capable of moving it, but finds it easier to walk with the three intact limbs. When both arms lose their sensations, the monkey is forced to rely on them.

Module 4.3 | End-of-Module Quiz

1. Which of these is one way in which a stroke kills neurons?
   - **a.** Decreased body temperature
   - **b.** Decreased supply of vitamin B-1
   - **c.** Excess GABA inhibition
   - **d.** Excess glutamate stimulation
2. How does tPA decrease damage from ischemia?
   - **a.** It increases myelination.
   - **b.** It increases body temperature.
   - **c.** It breaks up blood clots.
   - **d.** It increases neural excitation.
3. Which of these types of drugs decreases the damage from a stroke (if given promptly)?
   - **a.** Psychedelics
   - **b.** Cannabinoids
   - **c.** Antidepressants
   - **d.** Opiates
4. What causes diaschisis after a stroke?
   - **a.** Decreased input from damaged neurons
   - **b.** Lack of fluids
   - **c.** Competition between collateral sprouting and denervation supersensitivity
   - **d.** Overactivity of mitochondria

5. In which species, if any, can axons regrow in the spinal cord?

- **a.** Humans only
- **b.** Fish
- **c.** Birds
- **d.** No species

6. Where does collateral sprouting take place?

- **a.** In the cell body
- **b.** In the axon
- **c.** In the dendrites
- **d.** In both the axons and the dendrites

7. What causes the phantom limb experience?

- **a.** Irritation of receptors at the stump where the amputation occurred
- **b.** Spontaneous activity of receptors at the stump where the amputation occurred
- **c.** Reorganization of the sensory cortex
- **d.** A psychiatric reaction based on denial of the amputation

8. Suppose a patient uses only the right arm following injury that blocked sensation from the left arm. Of the following, which is most likely to encourage use of the left arm?

- **a.** Electrically stimulate the skin of the left arm.
- **b.** Tie the right arm behind the person's back.
- **c.** Blindfold the person.
- **d.** Increase visual stimulation on the right side of the body.

Answers: 1d, 2c, 3b, 4a, 5b, 6b, 7c, 8b.

Suggestions for Further Reading

Levi-Montalcini, R. (1988). *In praise of imperfection.* (Basic Books). Autobiography by the discoverer of nerve growth factor.

Ramachandran, V. S., and Blakeslee, S. (1998). *Phantoms in the brain.* (Morrow.) One of the most thought-provoking books ever written about human brain damage, including the phantom limb phenomenon.

Chapter 5

Later in this chapter, you will understand why this prairie falcon has tilted its head.

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Vision

Chapter Outline

Module 5.1

Visual Coding

Principles of Vision
The Eye and Its Connections to the Brain
Visual Receptors: Rods and Cones
Color Vision
In Closing: Visual Receptors

Module 5.2

Visual Processing in the Brain

An Overview of the Mammalian Visual System
Processing in the Retina
Further Processing
The Primary Visual Cortex
Development of the Visual Cortex
In Closing: Understanding Vision by Understanding the Wiring Diagram

Module 5.3

Specialized Visual Processes

The Ventral and Dorsal Streams
Shape Perception
Motion Perception
In Closing: Different Aspects of Vision

Learning Objectives

After studying this chapter, you should be able to:

1. Remember that we see because light strikes the retina, sending a message to the brain.
2. Describe the connections from the eyes to the brain and explain how they produce the blind spot of the eye.
3. List the properties of cones and rods.
4. Explain the main features of color vision.
5. Trace the route of visual information from the retina to the cerebral cortex.
6. Explain lateral inhibition in terms of the connections among neurons in the retina.
7. Define and give examples of receptive fields.
8. Describe research on how experiences alter development of the visual cortex.
9. Distinguish between the ventral and dorsal streams of the visual system.
10. Describe the brain mechanisms for perceiving shapes, faces, and movement.

Imagine that you are a piece of iron. There you are, sitting around doing nothing, as usual, when along comes a drop of water. What will be your perception of the water? Yes, a bar of iron doesn't have a brain, and it wouldn't have any perception at all. But let's ignore that inconvenient fact and imagine what it would be like if a bar of iron could perceive the water. From the standpoint of a piece of iron, water feels *rustish*.

Now return to your perspective as a human. You know that rustishness is not really a property of water itself but of how it reacts with iron. The same is true of human perception. Just as rust is how water affects the piece of iron, green is how a light affects your receptors. Green is in us, not in the light itself. We don't perceive the world itself, but only how certain aspects of the world interact with our receptors.

Module 5.1

Visual Coding

Learning Objectives

After studying this module, you should be able to:

1. Remember that we see because light strikes the retina, sending a message to the brain.
2. Describe the connections from the eyes to the brain and explain how they produce the blind spot of the eye.
3. List the properties of cones and rods.
4. Explain the main features of color vision.

Imagine that you have lived all your life in a room with no doors or windows. The temperature is carefully controlled, and a conveyor belt brings you the food and water that you need, but your only contact with the outside world is the text messages that a few observers send you. From that information, you try to imagine the world. Your observers tell you only what they think you might find useful. You have no way to check whether what they tell you is correct.

That scenario will sound far-fetched, but it is the situation facing your brain. Its contact with the outside world comes from the messages from your sense organs. Your eyes tell your brain about a limited range of electromagnetic radiation, your ears report a limited range of air waves, your taste buds detect a few types of chemicals, and so forth. As Donald Hoffman (2019) has forcefully argued, the sense organs' job is not to tell you the Truth about the world, but just to give you information that your evolutionary history found useful for your survival and reproduction. The colors you perceive, the sounds you hear, and the tastes and smells you experience are your brain's interpretation of the messages your receptors sent to you.

How does your brain use the sensory input? The 17th-century philosopher René Descartes believed that the nerves from the eye sent the brain a pattern of impulses arranged like a picture of the perceived object, right side up, as if a little person in the head was watching a screen. In fact, when you look at a triangle, the activity in your brain does not copy that shape, any more than a computer would arrange a series of 0s and 1s in the shape of a triangle.

Try It Yourself

Impulses in certain neurons indicate light, and impulses in others indicate sound, touch, or other sensations. In 1838, Johannes Müller described this insight as the **law of specific nerve energies**. Müller held that whatever excites a particular nerve establishes a special kind of energy unique to that nerve. Here is a demonstration: If you rub your eyes, you may see spots or flashes of light even in a totally dark room. The mechanical pressure excited visual receptors in your eyes, and anything that excites those receptors is perceived as light. (If you try this demonstration, first remove any contact lenses. Shut your eyelids and rub gently.)

In modern terms, the brain interprets the action potentials from the auditory nerve as sounds, those from the olfactory nerve as odors, and so forth. Why you experience activity in one set of neurons as sound and another as odor is a deep question. The neurons look nearly the same, after all.

Stop & Check

1. If someone electrically stimulated the auditory receptors in your ear, what would you perceive?
2. If it were possible to flip your entire brain upside down without breaking any of the connections to sense organs, what would happen to your perceptions of what you see, hear, and so forth?

See page 159 for the answer.

Principles of Vision

Several decades ago, a graduate student taking his final oral exam for a PhD in psychology was asked, "How far can an ant see?" He turned pale. He did not know the answer, and evidently he was supposed to. He tried to remember everything he knew about insect vision. Finally, he gave up and admitted he did not know.

With an impish grin, the professor told him, "Presumably, an ant can see 93 million miles—the distance to the sun." Yes, this was a trick question, but it illustrates an important point: How far an ant sees, or how far you see, depends only on how far the light travels before it strikes the eyes. You do not send out "sight rays." That principle was probably the first scientific discovery in psychology (Steffens, 2007). Philosopher Hasan Ibn al-Haytham (965–1040) observed that when you open your eyes at night, you immediately see the distant stars. He reasoned that if you saw by sending out sight rays, they couldn't get to the stars that fast. Then he demonstrated that light rays bounce off an object in all directions, but you see only those rays that reflect off the object and strike your retina (Gross, 1999).

The point is worth emphasizing, because a distressingly large number of college students believe they send out sight rays from their eyes when they see (Winer et al., 2002). Even some students who have taken courses in physics or visual perception continue to hold that deep misunderstanding. This is one of the most important principles to remember from this text: When you see a tree, your perception is not in the tree. It is in your brain. You see something only when light from it alters your brain activity. Even if you did send out rays from your eyes—and you don't—when they struck some object, you wouldn't know about it, unless they bounced back and returned to your eyes.

Similarly, you feel something only when touch information reaches your brain. You feel something *with* your fingers, but you don't feel it *in* your fingers. You feel it in your brain.

Stop & Check

3. What was Ibn al-Haytham's evidence that we see only because light enters the eyes, not by sending out sight rays?

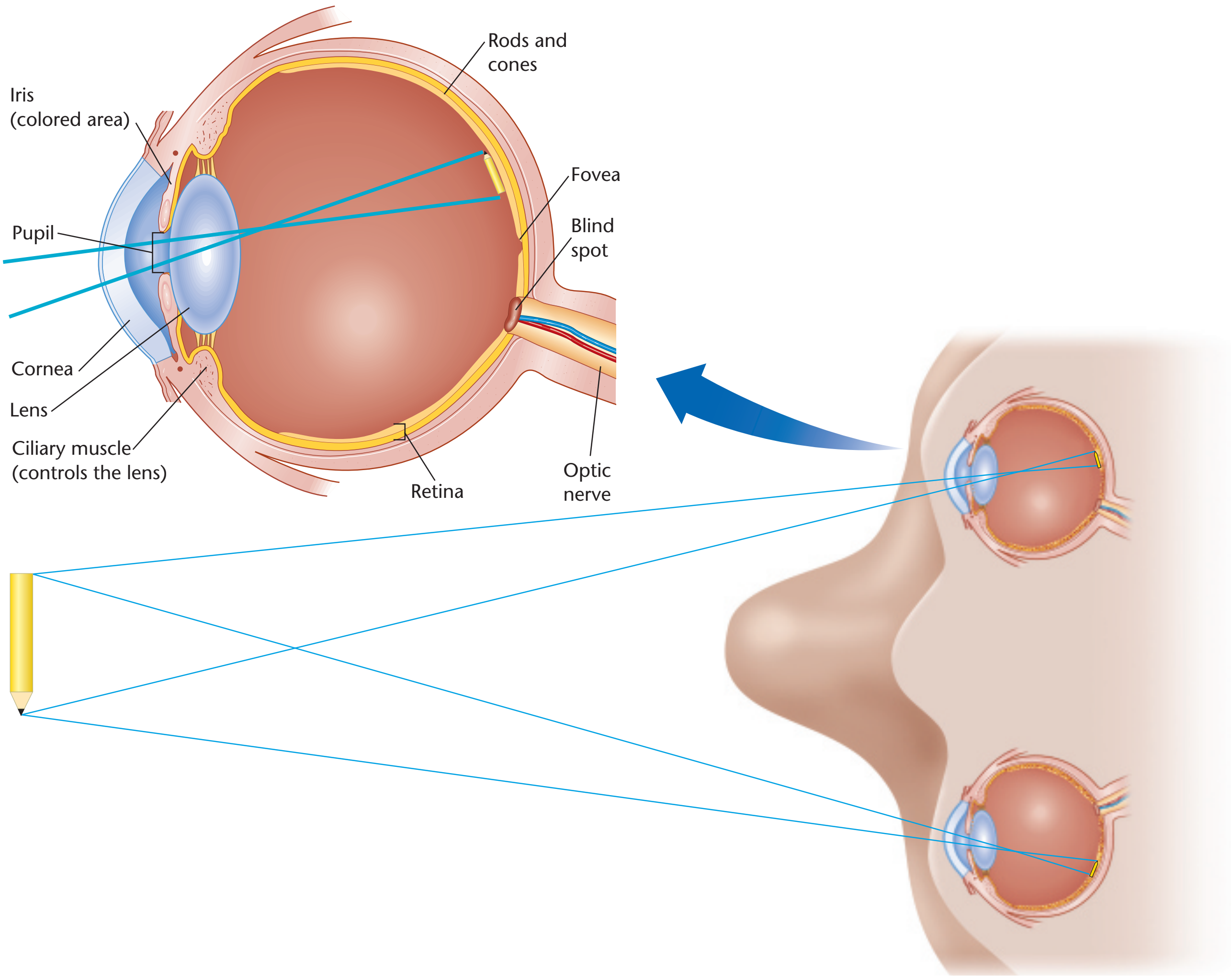
See page 159 for the answer.

The Eye and Its Connections to the Brain

Light enters the eye through an opening in the center of the iris called the **pupil** (Figure 5.1). It is focused by the lens (adjustable) and cornea (not adjustable) and projected onto the **retina**, the rear surface of the eye, which is lined with visual

Figure 5.1 Cross-section of the vertebrate eye

An object in the visual field produces an inverted image on the retina. The optic nerve exits the eyeball on the nasal side (the side closer to the nose).



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receptors. Light from the left side of the world strikes the right half of the retina, and vice versa. Light from above strikes the bottom half of the retina, and light from below strikes the top half. The inversion of the image poses no problem for the nervous system. Remember, the visual system does not duplicate the image. It codes it by various kinds of neuronal activity. If you find this idea puzzling, think about a computer. A computer chip that codes what to display at the upper left of your screen does not need to be in the upper left of the computer.

Route within the Retina

If you were designing an eye, you would probably send the receptors' messages directly back to the brain. In the vertebrate retina, however, messages go from the receptors at the back of the eye to **bipolar cells**, located closer to the center of the eye (Figure 5.2). The bipolar cells send their messages to **ganglion cells**, located still closer to the center of the eye. The ganglion cells' axons unite and travel back to the brain as the optic nerve (Figure 5.3). Additional cells called *amacrine cells* get information from bipolar cells and send it to bipolar cells, ganglion cells, and other amacrine cells. Amacrine cells refine the responses of bipolar and ganglion cells, enabling certain ones to respond mainly to shapes, directions of movement, color, or other visual features (Franke et al., 2017).

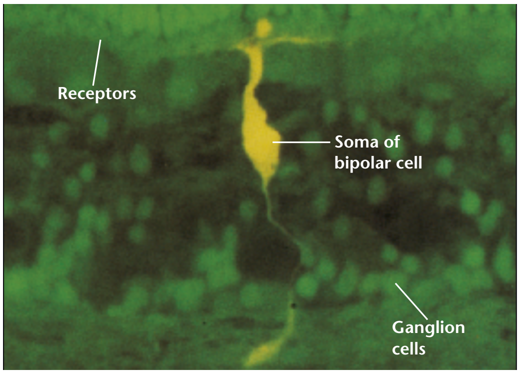
One consequence of this anatomy is that light passes through the ganglion, amacrine, and bipolar cells en route to the receptors. Because these cells are transparent, light passes through them without significant distortion. A more important consequence is the *blind spot*. The ganglion cell axons join to form the **optic nerve** that exits through the back of the eye. The point at which it leaves (also where the blood vessels enter and leave) is a **blind spot** because it has no receptors.

Try It Yourself

You can demonstrate your own blind spot with Figure 5.4. Close your left eye and focus your right eye on the top o. Then move the page forward and back. When the page is about 10 inches (25 cm) away, the x disappears because its image strikes the blind spot.

Figure 5.2 A bipolar cell from the retina of a carp, stained yellow

Bipolar cells get their name from the fact that a fibrous process is attached to each end (or pole) of the neuron.



(**Source:** Dowling, 1987)

Now repeat with the lower part of the figure. When the page is again about the same distance from your eyes, what do you see? The *gap* disappears! When the blind spot interrupts a straight line or other regular pattern, your brain fills in the gap.

Try It Yourself

In everyday life, you never notice your blind spot, for two reasons. First, your brain fills in the gap, as you just experienced. Second, anything in the blind spot of one eye is visible to the other eye. Use Figure 5.4 again to locate the blind spot in your right eye. Then close your right eye and open the left one. You will see the spot that the right eye couldn't see.

Stop & Check

4. What makes the blind spot of the retina blind?

See page 159 for the answer.

Fovea and Periphery of the Retina

When you look at details such as the letters on this page, you fixate them on the central portion of your retina, especially the **fovea** (meaning "pit"), a tiny area specialized for acute, detailed vision (Figure 5.1). Because blood vessels and ganglion cell axons are almost absent near the fovea, it has nearly unimpeded vision. The tight packing of receptors aids perception of detail.

More importantly for perceiving detail, each receptor in the fovea connects to a single *bipolar cell*, which in turn connects to a single *ganglion cell* that has an axon to the brain. The ganglion cells in the fovea of humans and other primates are called **midget ganglion cells** because each is small and responds to just a single cone. That is, each cone in the fovea has a direct route to the brain. Because the midget ganglion cells provide 70 percent of the input to the brain, your vision is dominated by what you see in and near the fovea (Nassi and Callaway, 2009).

You have heard the expression "eyes like a hawk." Many birds' eyes occupy most of the head, compared to 5 percent of a human's head. Furthermore, many bird species have two fovea-like areas per eye, one pointing ahead and one pointing to the side (Wallman and Pettigrew, 1985). The result enables perception of detail in the periphery. Elephants, rhinoceroses, and hippopotamuses have two or three highly acute zones in each retina. A likely explanation is that these huge animals would have trouble turning their heads quickly to see something coming from the side (Baden et al., 2020).

Hawks and other predatory birds have a greater density of visual receptors on the top half of their retinas (looking down) than on the bottom half (looking up). That arrangement is adaptive because predatory birds spend most of their day looking down, either while flying or while perched high in a tree. To look up, the bird must turn its head, as in Figure 5.5 (Waldvogel, 1990). Conversely,

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Figure 5.3 Visual path within the eye

Receptors send their messages to bipolar and horizontal cells, which in turn send messages to amacrine and ganglion cells. The axons of the ganglion cells form the optic nerve, which exits the eye at the blind spot and continues to the brain.

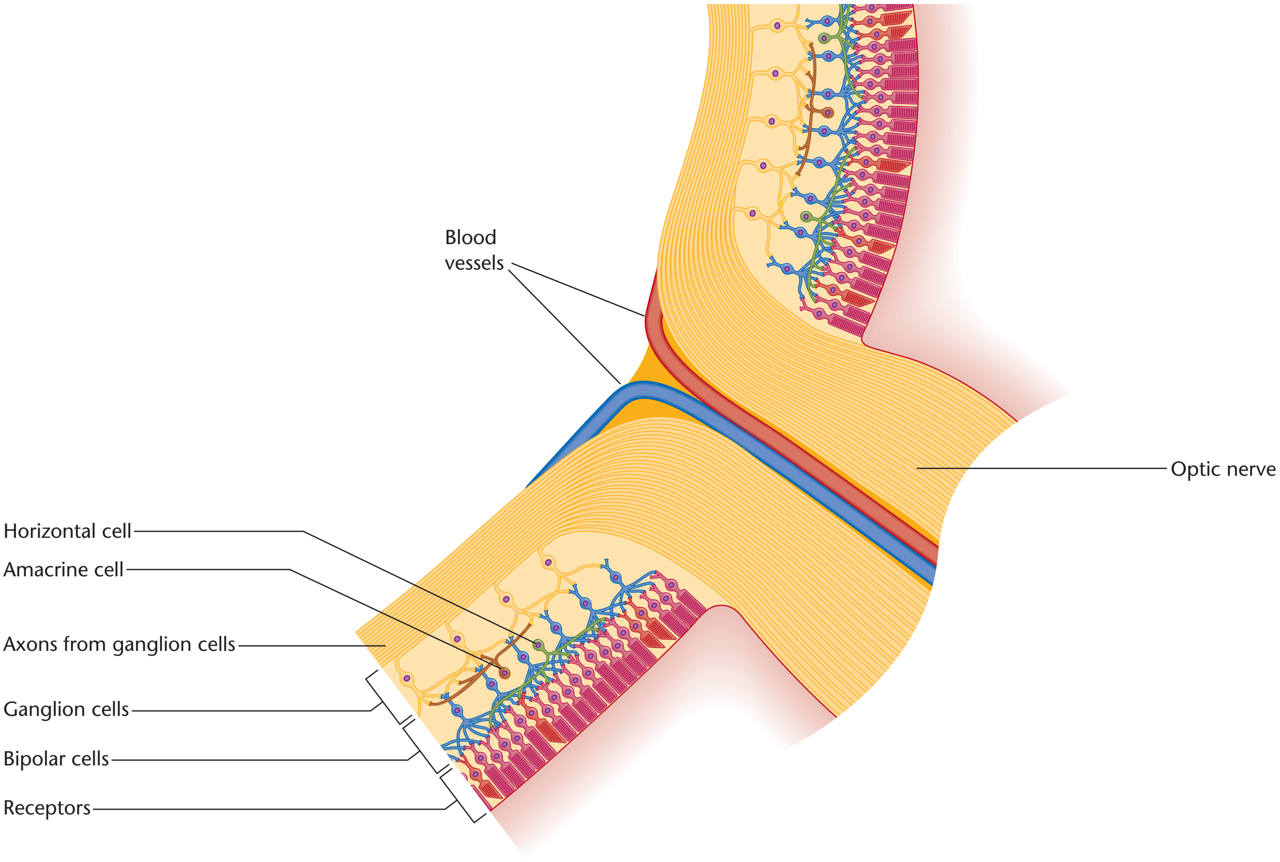


Figure 5.4 Demonstrations of the blind spot of the retina

Close your left eye and focus your right eye on the o in the top part. Move the page toward you and away, noticing what happens to the x. At a distance of about 10 inches (25 cm), the x disappears. Now repeat this procedure with the bottom part. At that same distance, what do you see?

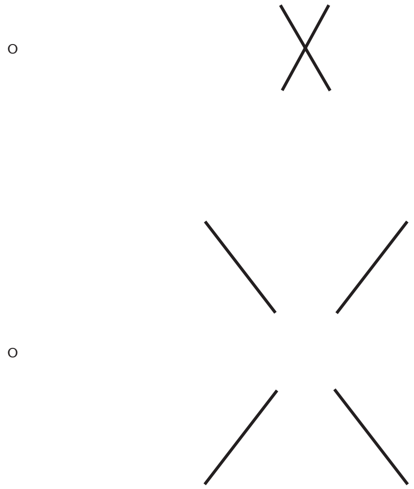
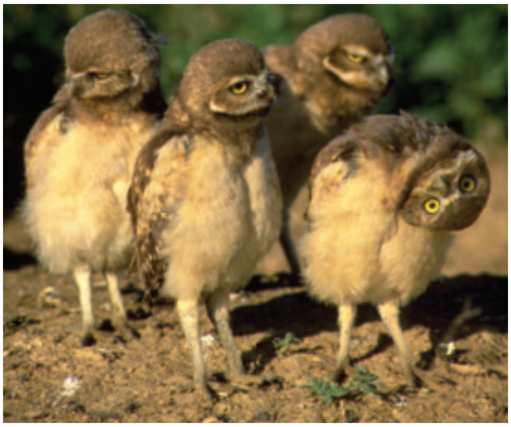


Figure 5.5 A consequence of how receptors are arranged on the retina

One owlet has turned its head almost upside down to look up. Birds of prey have many receptors on the upper half of the retina, enabling them to see down in great detail during flight. But they see objects above themselves poorly unless they turn their heads. Think about the prairie falcon at the start of this chapter. Do you now understand why the bird tilted its head?



(**Source:** Chase Swift/The Image Bank/Getty Images)

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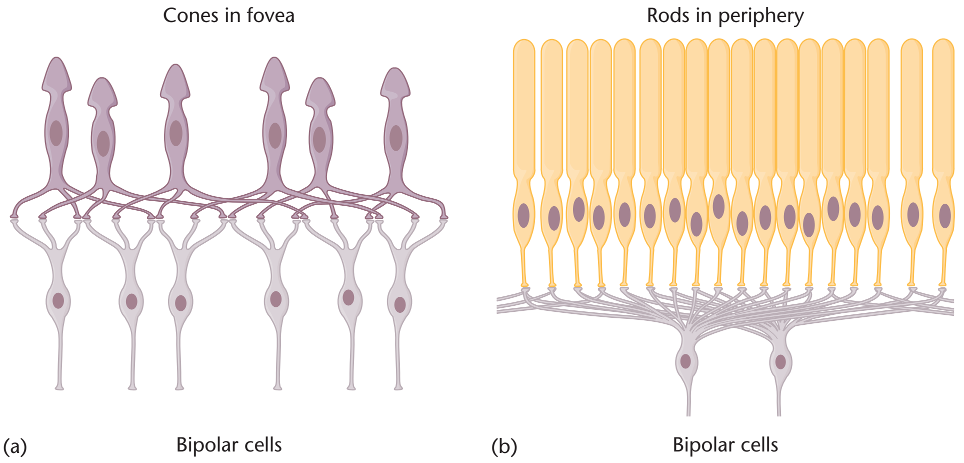
Figure 5.6 Convergence of input onto bipolar cells

In the fovea, each bipolar cell receives excitation from just one cone (and inhibition from a few surrounding cones), and it relays its information to a single midget ganglion cell. In the periphery, input from many rods converges onto each bipolar cell, resulting in higher sensitivity to faint light and low sensitivity to spatial location.



many prey species such as rats have most of their receptors on the bottom half of the retina, enabling them to see up better than they see down (Lund et al., 1974). You can see the evolutionary advantages for these species.

Toward the periphery of the retina, more and more receptors converge onto bipolar and ganglion cells, as depicted in Figure 5.6. The summation enables perception of fainter lights in the periphery. However, feeding so many receptors into the same bipolar or ganglion cell loses information about the exact shape or location of an object (Rossi and Roorda, 2010). We ordinarily have the impression that we see the whole scene in front of us. In fact, we see clearly only the small portion that focuses on the fovea. To the extent that we know what is in the rest of the scene, we are relying mostly on memory.

Try It Yourself

In the periphery, your ability to detect detail is limited by interference from other nearby objects (Pelli and Tillman, 2008). In the displays below, focus on the x. For the first display, you can probably identify the letter to the right. For the second display, it is harder to read that same letter in the same location, because of interference from the neighboring letters. In summary, foveal vision has better *acuity* (sensitivity to detail), and peripheral vision has better sensitivity to dim light. Perception of movement is about the same for fovea and periphery.

X T

X ATE

Visual Receptors: Rods and Cones

The vertebrate retina has two types of receptors: rods and cones (Figure 5.7). The **rods**, abundant in the periphery of the human retina, respond to faint light but are less useful in daylight because bright light bleaches them. **Cones**, abundant in and near the fovea, are more useful in bright light and essential for color vision. Because of the distribution of rods and cones, humans have good color vision in the fovea but not in the periphery. Table 5.1 summarizes the differences between foveal and peripheral vision.

Although rods outnumber cones by about 20 to 1 in the human retina, cones provide about 90 percent of the brain's input (Masland, 2001). Remember the midget

Table 5.1 | Human Foveal and Peripheral Vision

Characteristic	Foveal Vision	Peripheral Vision
Receptors	Cones only	Proportion of rods increases toward periphery
Convergence of input	Each ganglion cell excited by a single cone	Each ganglion cell excited by many receptors
Brightness sensitivity	Distinguishes among bright lights; responds poorly to dim light	Responds to dim light; poor for distinguishing among bright lights
Sensitivity to detail	Good detail vision because each cone's midget ganglion cell sends a message to the brain	Poor detail vision because many receptors converge their input onto a given ganglion cell
Color vision	Good (many cones)	Poor (few cones)

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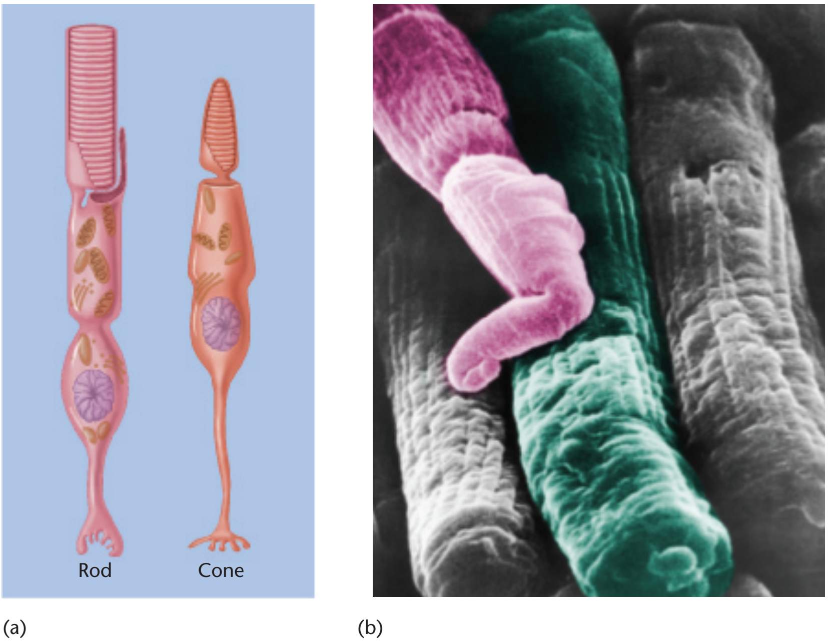
Figure 5.7 Structure of rod and cone

(a) Diagram of a rod and a cone. (b) Photo of rods and a cone, produced with a scanning electron microscope, with color added artificially



Omikron/Science Source

(**Source:** Reprinted from "Scanning electron microscopy of vertebrate visual receptors," by E. R. Lewis, Y. Y. Zeevi, and F. S. Werblin, Brain Research, 15 (2), with permission of Elsevier.)

Agami Photo Agency/Shutterstock.com

An oilbird pair sitting on their nest in a cave in Ecuador. These nocturnal birds have some 15,000 rods per cone in their eyes.

ganglion cells: In the fovea, each cone has its own line to the brain. In the periphery (mostly rods), each receptor shares a line with tens or hundreds of others. Overall, 120 million rods and 6 million cones converge onto 1 million axons in the optic nerve, on average.

A 20:1 ratio of rods to cones may sound high, but the ratio is even higher in species that are active at night. South American oilbirds, which live in caves and emerge only at night, have about 15,000 rods per cone. As further adaptations to detect faint lights, they have large pupils and their rods are packed three deep throughout the retina (G. Martin et al., 2004). Some deep-sea fish also have specializations for detecting the tiny amount of light that reaches them (Musilova et al., 2019).

People vary substantially in the number of axons in their optic nerve and the size of the visual cortex, largely for genetic reasons (Bakken et al., 2012). Some people have two or three times as many axons from the eyes to the brain as others do. They also have more cells in their visual cortex (Andrews et al., 1997; Stevens, 2001; Sur and Leamey, 2001) and greater ability to detect brief, faint, or rapidly changing visual stimuli (Halpern et al., 1999). Heightened visual responses are valuable in many activities, especially in sports that require aim. Researchers find that top performers in tennis, squash, fencing, baseball, and badminton demonstrate enhanced processing of visual stimuli, compared to other people (Muraskin et al., 2015; Nakata et al., 2010; C.-H. Wang et al., 2015). Excellent vision is hardly the only ingredient for athletic success, but it helps.

Both rods and cones contain **photopigments**, chemicals that release energy when struck by light. Photopigments consist of 11-*cis*-retinal (a derivative of vitamin A) bound to proteins called *opsins*, which modify the photopigments' sensitivity to different wavelengths of light. Light converts 11-*cis*-retinal to all-*trans*-retinal, thus releasing energy that activates second messengers within the cell (Q. Wang et al., 1994). (The photopigment absorbs the light. The light does not bounce around the eye.)

Stop & Check

5. You sometimes find that you can see a faint star on a dark night better if you look slightly to the side of the star instead of straight at it. Why?
6. If you found a species with a high ratio of cones to rods in its retina, what would you predict about its way of life?

See page 159 for the answer.

Color Vision

Visible light consists of electromagnetic radiation within the range from less than 400 nm (nanometer, or 10^{-9} m) to more than 700 nm. We perceive the shortest visible wavelengths as violet. Progressively longer wavelengths

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are perceived as blue, green, yellow, orange, and red (Figure 5.8). We call these wavelengths "light" only because the receptors in our eyes are tuned to detecting them. If we had different receptors, we would define light differently. Indeed, many species of birds, fish, and insects have visual receptors sensitive to what we call ultraviolet radiation (Bowmaker, 2008; Stevens and Cuthill, 2007). We cannot know what it looks like to them, but so far as they are concerned, ultraviolet radiation is a type of light. In some species of birds, the male and female look alike to us, but the birds see a difference, because the male reflects more ultraviolet light. Birds would regard us as partly colorblind.

The Trichromatic (Young-Helmholtz) Theory

People distinguish red, green, yellow, blue, orange, pink, purple, greenish blue, and so forth. Presuming that we don't have a separate receptor for every possible color, how many receptor types do we have?

Among those who helped to advance our understanding on this question was an amazingly productive man named Thomas Young (1773–1829), who founded the modern wave theory of light, defined energy in its modern form, founded the calculation of annuities, introduced the coefficient of elasticity, discovered much about the anatomy of the eye, and made major contributions to other fields (Martindale, 2001). Previous scientists thought they could explain color by understanding the physics of light. Young recognized that color required a biological explanation. He proposed that we perceive color by comparing the responses across a few types of receptors, each of which was sensitive to a different range of wavelengths.

This theory, later modified by Hermann von Helmholtz, is now known as the **trichromatic theory** of color vision, or the **Young-Helmholtz theory**. According to this theory, we perceive color through the relative rates of response by three kinds of cones, each one maximally sensitive to a different set of wavelengths. (*Trichromatic* means "three colors.") How did Helmholtz decide on the number three? He found that people could match any color by mixing appropriate amounts of just three wavelengths. Therefore, he concluded that three kinds of receptors—we now call them cones—are sufficient to account for human color vision.

Figure 5.9 depicts wavelength-sensitivity functions for the *short-wavelength*, *medium-wavelength*, and *long-wavelength* cone types. Each cone responds to a broad range of wavelengths but to some more than others.

According to the trichromatic theory, humans discriminate among wavelengths by the ratio of activity across the three types of cones. For example, light at 550 nm excites the medium-wavelength and long-wavelength receptors about equally and the short-wavelength receptor almost not at all. This ratio of responses among the three cones determines a perception of yellow-green. More intense light increases the activity of all three cones without much change in their ratio of responses. As a result, the light appears brighter but still the same color. When all three types of cones are equally active, we see white or gray.

Think about this example of coding: Your perception of color depends on the frequency of response in each cell *relative to* the frequency of other cells. The response of any one cone is ambiguous. For example, a low response rate by a middle-wavelength cone might indicate low-intensity 540 nm light or brighter 500 nm light or still brighter 460 nm light. The nervous system determines the color of the light by comparing the responses of different types of cones.

Given the desirability of seeing all colors in all locations, we might suppose that the three kinds of cones would be equally abundant and evenly distributed. In fact, they are not. Long- and medium-wavelength cones are far more abundant than short-wavelength (blue) cones. Consequently, it is easier to see tiny red, yellow, or green dots than blue dots (Roorda and Williams, 1999). Try this: Look

Figure 5.8 A beam of light separated into its wavelengths

Although the wavelengths vary as a continuum, we perceive distinct colors.

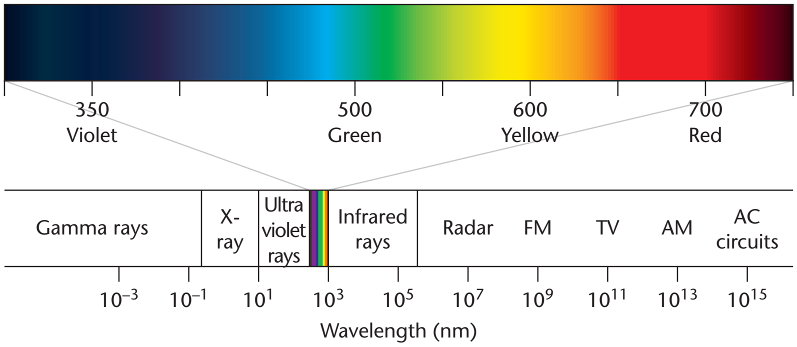
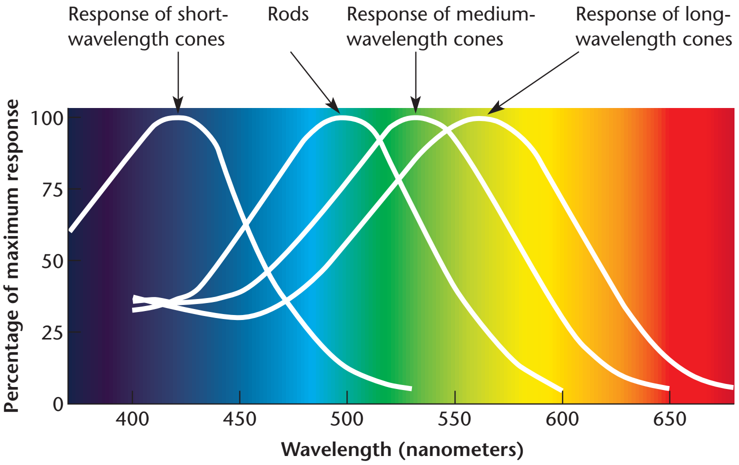


Figure 5.9 Responses of rods and three kinds of cones

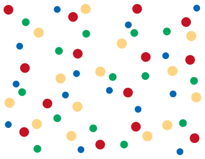
Note that each kind responds somewhat to a wide range of wavelengths but best to wavelengths in a particular range.



(**Source:** Adapted from Bowmaker and Dartnall, 1980)

at the dots in the following display, first from close and then from greater distances. You probably will notice that the blue dots look blue when they are close to you but they appear black from a greater distance. The other colors remain visible when the blue is not.

Try It Yourself



Although the short-wavelength (blue) cones are about evenly distributed across the retina, the other two kinds are distributed haphazardly, with big differences among individuals (Solomon and Lennie, 2007; Zhang et al., 2019). Because of the haphazard arrangement, moderate-sized patches of the retina have only medium- or long-wavelength cones (Roorda and Williams, 1999). Some people have more than 10 times as many of one kind as the other. Surprisingly, these variations produce only small differences in people's color perceptions (Solomon and Lennie, 2007).

In the retina's periphery, cones are so scarce that you have no useful color vision (Diller et al., 2004; P. R. Martin et al., 2001). Try this: Get someone to put a colored dot on the tip of your finger without telling you the color. A spot of colored ink will do. While keeping your eyes straight ahead, slowly move your finger from behind your head into your field of vision and gradually toward your fovea. At what point do you first see your finger? At what point do you see the color? You will see your finger before you see the color. The smaller the dot, the farther you need to move it into your **visual field** —that is, the part of the world that you see—before you can identify the color.

Try It Yourself

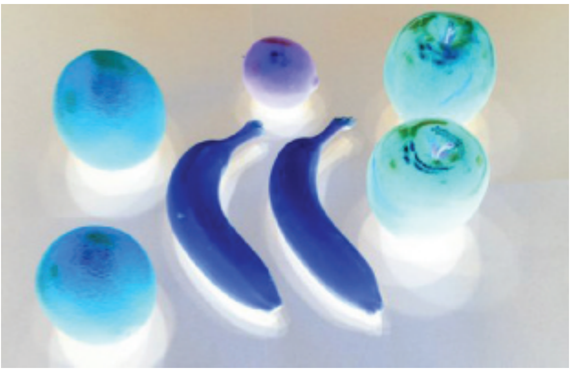
The Opponent-Process Theory

The trichromatic theory is incomplete as a theory of color vision. For example, try the following demonstration: Pick a point near the center of Figure 5.10 and stare at it under a bright light, without moving your eyes, for a minute. (The brighter the light and the longer you stare, the stronger the effect.) Then look at a plain white surface, such as a wall or a blank sheet of paper. Keep your eyes steady. You will see a **negative color afterimage**, a replacement of the red you had been staring at with green, green with red, yellow and blue with each other, and black and white with each other.

Try It Yourself

Figure 5.10 Stimulus for demonstrating negative color afterimages

Stare at one point under bright light for about a minute, without moving your eyes, and then look at a white field. You should see two oranges, a lime, two bananas, and two apples, all in their normal color.



Jo Ellen Kalat

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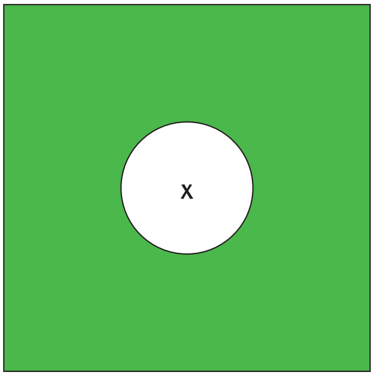
To explain this and related phenomena, Ewald Hering, a 19th-century physiologist, proposed the **opponent-process theory**: We perceive color in terms of opposites (Hurvich and Jameson, 1957). That is, the brain has a mechanism that perceives color on a continuum from red to green, another from yellow to blue, and another from white to black. After you stare at one color in one location long enough, you fatigue that response and tend to swing to the opposite.

Part of the explanation for this process pertains to the connections within the retina. For example, imagine a bipolar cell that receives excitation from medium-wavelength cones and inhibition from long-wavelength cones. It increases its activity in response to medium-wavelength (green) light and decreases it in response to reddish light. After prolonged exposure to green light, the fatigued cell decreases its response. Because a low level of response by that cell usually means red, you perceive red. When researchers around 1950 first demonstrated that certain cells increased their activity in response to one wavelength of light and decreased it to another, they revolutionized our understanding of vision, and of the nervous system in general (Jacobs, 2014).

However, the explanation must go beyond the connections from cones to the bipolar cells. Try this: Stare at the x in the following diagram for a minute or more under a bright light and then look at a white page.

Try It Yourself



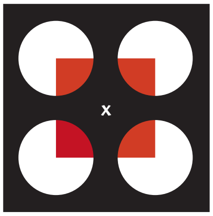
For the afterimage of the surround, you saw red, as the theory predicts. But what about the circle inside? Theoretically, you should see a gray or black afterimage (the opposite of white), but in fact, if you used a bright enough light, you saw a green afterimage. What you saw in the surround influenced what you saw in the center.

Here is another demonstration: First, refer to Figure 5.11. Note that although it depicts four red quarter circles, you have the illusion of a whole red square. (Look carefully to convince yourself that it is an illusion.) Now stare at the x in Figure 5.11 for at least a minute under bright lights. Then look at a white surface.

Try It Yourself

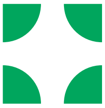
Figure 5.11 An afterimage hard to explain in terms of the retina

Stare at the x under bright light for a minute and then look at a white surface. Many people report an alternation between two afterimages, one of them based on the illusion of a red square.

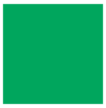


(Reprinted with permission from S. Shimojo, Y. Kamitani, and S. Nishida. Afterimage of perceptually filled-in surface, *Science*, 293, 1677–1680, specifically Figure 1A, p. 1678 [left hand]. Copyright 2001 American Association for the Advancement of Science.)

People usually report that the afterimage fluctuates. Sometimes, they see four green quarter circles:



And sometimes, they see a whole green square (Shimojo et al., 2001):



If you see a whole green square, it is the afterimage of an illusion! The red square you "saw" wasn't really there. This demonstration suggests that afterimages depend on the whole context, not just the light on individual receptors. The visual system must be comparing inputs over a substantial area, not just the cells connected to a particular bipolar or ganglion cell.

Stop & Check

7. Examine Figure 5.9. According to the trichromatic theory, what causes you to perceive red?
8. According to the opponent-process theory, under what circumstance would you perceive a white object as blue?

See page 159 for the answer.

The Retinex Theory

Neither the trichromatic theory nor the opponent-process theory can easily explain **color constancy**, the ability to recognize colors despite changes in lighting (Kennard et al., 1995; Zeki, 1980, 1983). If you wear green-tinted glasses or replace your white lightbulb with a green one, you still identify bananas as yellow, paper as white, and so forth. Your brain compares the color of one object with the color of another, in effect subtracting a certain amount of green from each.

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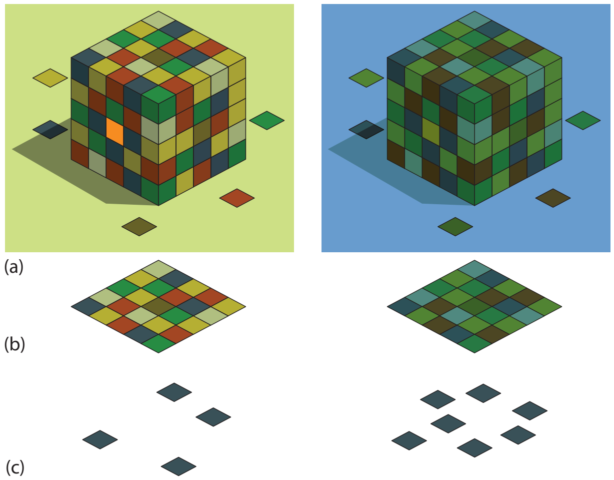
Figure 5.12 Effects of context on color perception

After removal of the context, squares that appeared blue on the left or yellow on the right now appear gray.



(**Source:** From Why we see what we do, by D. Purves and R. B. Lotto, Figure 5.10, p. 155. Copyright 2003 Sinauer Associates, Inc. Reprinted by permission.)

To illustrate, examine Figure 5.12 (Purves and Lotto, 2003). Although different colors of light illuminate the two objects at the top, you easily identify the squares as red, yellow, blue, and so forth. Note the result of removing context. The bottom part illustrates the squares that looked blue in the top left part and yellow in the top right part. Without the context that indicated yellow light or blue light, all these squares look gray. For this reason, we should be cautious about talking about the color of a wavelength of light. A certain wavelength of light can change color depending on the background.

Similarly, we perceive the brightness of an object by comparing it to other objects. Examine Figure 5.13 (Purves et al., 1999). The object in the center appears to have a dark gray top and a white bottom. Now cover the border between the top and the bottom with a finger. You see that the top of the object has the same brightness as the bottom!

Try It Yourself

To account for color and brightness constancy, Edwin Land proposed the **retinex theory** (a combination of the words *retin*a and cort*ex*): The cortex compares information from various parts of the retina to determine the brightness and color for each area (Land et al., 1983).

Dale Purves and colleagues have expressed a similar idea in more general terms: Whenever we see anything, we make an inference. For example, when you look at the objects in Figures 5.12 and 5.13, you ask yourself, "On occasions when I have seen something that looked like this, what was it really?" You go through the same process for perceiving shapes, motion, or anything else (Lotto and Purves, 2002; Purves and Lotto, 2003). That is, visual perception is a process of reasoning and inference, not just retinal stimulation.

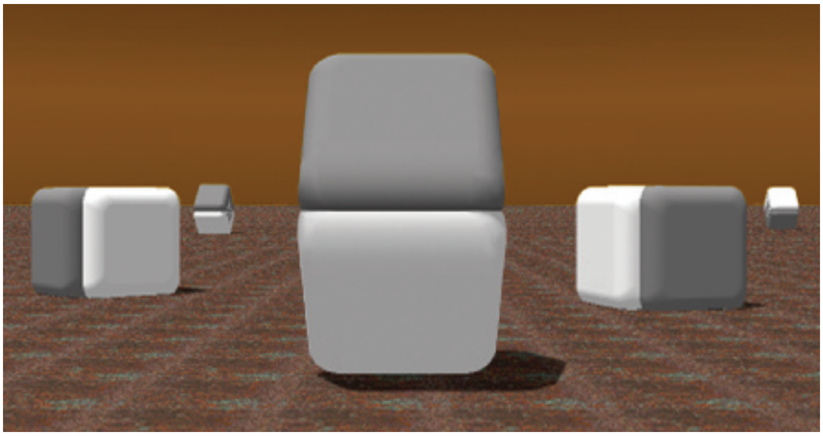
Stop & Check

9. When a television set is off, its screen appears gray. When you watch a program, parts of the screen appear black, even though the screen is displaying more light than when the set was off. What explains the black perception?
10. Figure 5.9 illustrates light at about 510 nm as green. Why should we nevertheless not call it "green light"?

See page 160 for the answer.

Figure 5.13 Brightness constancy

In the center of this figure, do you see a gray object above and a white object below? Place a finger over the border between them and then compare the objects.



(**Source:** From "An empirical explanation of cornsweet effect," by D. Purves, A. Shimpi, and R. B. Lotto, *Journal of Neuroscience, 19,* pp. 8542–8551. Copyright 1999 by the Society for Neuroscience.)

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Color Vision Deficiency

One of the first discoveries in psychology was colorblindness, better described as **color vision deficiency**. (Complete colorblindness, perception of only black and white, is rare.) Today we are familiar with the idea that some people see color better than others do, but before the 1600s, people assumed that everyone sees the same way, and that what we perceive is what the object actually *is* (Fletcher and Voke, 1985). Then investigators demonstrated that some people have otherwise satisfactory vision without seeing all the color that other people do. That is, color is in the brain, not in the light or the object itself.

Color vision deficiency results when people with certain genes fail to develop one type of cone, or develop an abnormal type of cone (Nathans et al., 1989). In red-green color deficiency, the most common form of color deficiency, people have trouble distinguishing red from green because their long- and medium-wavelength cones have the same photopigment instead of different ones. The gene causing this deficiency is on the X chromosome. About 8 percent of Northern European men (and a smaller percentage of men from other backgrounds) are red-green colorblind, compared with less than 1 percent of women (Bowmaker, 1998). Women with one normal gene and one color-deficient gene—and that includes all women with a father with red-green color deficiency—have slightly less than average ability to distinguish red from green (Bimler and Kirkland, 2009).

Suppose we could transplant the missing cones to an adult with a red-green deficiency. Would the brain start seeing in full color? No one has tested this question for people, but we do know what would happen for monkeys. Researchers took adult monkeys with red-green color deficiency and used gene therapy to add a third kind of cone to their retinas. They quickly learned to discriminate red from green (Mancuso et al., 2009). Evidently, the brain adapts to use the information it receives.

What would happen if people had a fourth type of cone? Some women do, in a way. The long-wavelength cone displays genetic variation. At one point in this cone's receptor protein, most genes code for the amino acid *serine*, but 16 to 38 percent of the genes (depending on people's ethnic background) produce instead the amino acid *alanine*. Because the gene is on the X chromosome, a man has only one or the other. Because women have two X chromosomes, some women have one receptor with serine and one with alanine. Those two versions of the long-wavelength receptor differ slightly in their responsiveness to light (Deeb, 2005). Women with two versions of that receptor make somewhat finer than average distinctions between one color and another (Jameson et al., 2001).

Stop & Check

11. Why is color vision deficiency a better term than color blindness?

See page 160 for the answer.

Module 5.1 | In Closing

Visual Receptors

I remember once explaining to my then teenage son a newly discovered detail about the visual system, only to have him reply, "I didn't realize it would be so complicated. I thought the light strikes your eyes and then you see it." As you should now be starting to realize—and if not, the rest of the chapter should convince you—vision requires complicated processing. If you tried to equip a robot with vision, you would quickly discover that shining light into its eyes accomplishes nothing, unless its visual detectors are connected to devices that identify the useful information and use it to select the proper action. We have such devices in our brains, and they produce the amazing results that we call vision.

Summary

1. Sensory information is coded so that the brain can process it. The coded information does not physically resemble the stimuli it describes. **148**
2. According to the law of specific nerve energies, the brain interprets any activity of a given sensory neuron as representing a particular type of sensory information. **148**
3. You see because light strikes your retina, causing it to send a message to your brain. You send no sight rays out to the object. **148**
4. Light passes through the pupil of a vertebrate eye and stimulates the receptors lining the retina at the back of the eye. **149**

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5. The axons from the retina loop around to form the optic nerve, which exits from the eye at a point called the blind spot. **150**
6. Visual acuity is greatest in the fovea, the central area of the retina. Because so many receptors in the periphery converge their messages to their bipolar cells, our peripheral vision is highly sensitive to faint light but poorly sensitive to detail. **150**
7. The retina has two kinds of receptors: rods and cones. Rods, more numerous in the periphery of the retina, are more sensitive to faint light. Cones, more numerous in the fovea, are more useful in bright light. **152**
8. People vary in their number of axons from the retina to the brain. Those with more axons demonstrate a greater ability to detect brief, faint, or rapidly changing stimuli. **153**
9. According to the trichromatic (or Young-Helmholtz) theory of color vision, color perception begins with a given wavelength of light stimulating a distinctive ratio of responses by the three types of cones. **154**
10. According to the opponent-process theory of color vision, visual system neurons beyond the receptors respond with an increase in activity to indicate one color of light and a decrease to indicate the opposite color. The three pairs of opposites are red-green, yellow-blue, and white-black. **155**
11. According to the retinex theory, the cortex compares the responses across the retina to determine brightness and color of each object. **156**
12. For genetic reasons, certain people are unable to distinguish one color from another. Red-green color deficiency is the most common type. **158**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

bipolar cells	**150**
blind spot	**150**
color constancy	**156**
color vision deficiency	**158**
cones	**152**
fovea	**150**
ganglion cells	**150**
law of specific nerve energies	**148**
midget ganglion cells	**149**
negative color afterimage	**155**
opponent-process theory	**156**
optic nerve	**150**
photopigments	**153**
pupil	**149**
retina	**149**
retinex theory	**157**
rods	**152**
trichromatic theory (or Young-Helmholtz theory)	**154**
visual field	**155**

Thought Question

How could you test for the presence of color vision in a bee? Examining the retina does not help because invertebrate receptors resemble neither rods nor cones. It is possible to train bees to approach one visual stimulus and not another. However, if you train bees to approach, say, a yellow card and not a green card, you do not know whether they solved the problem by color or by brightness. Because brightness is different from physical intensity, you cannot assume that two colors equally bright to humans are also equally bright to bees. How might you get around the problem of brightness to test color vision in bees?

Stop & Check Answers

1. Because of the law of specific nerve energies, you would perceive it as sound, not as shock. (Of course, a strong enough shock might spread far enough to excite pain receptors also.)
2. Your perceptions would not change. The way visual or auditory information is coded in the brain does not depend on the physical location within the brain. Seeing something as "on top" or "to the left" depends on which neurons are active but does not depend on the physical location of those neurons.
3. First, you can see distant objects such as stars far faster than any sight rays could reach them. Second, when light strikes an object, we see only the light rays that reflect off the object and into the eyes.
4. The blind spot has no receptors because it is occupied by exiting axons and blood vessels.
5. If you look slightly to the side, the light falls on an area of the retina with more rods and more convergence of input.
6. We should expect this species to be highly active during the day and seldom active at night.
7. Activity of the long-wavelength cone is not sufficient. In fact, notice that the long-wavelength cone responds to what we call yellow more than to what we call red. A perception of red occurs only if the long-wavelength cone has a high ratio of response relative to the other two types of cone.
8. If you stared at a bright yellow object for a minute or so and then looked at a similar white object, it would appear blue.
9. The black experience arises by contrast with the surrounding areas that are brighter.

10. Color perception depends not just on the wavelength of light from a given spot but also the light from surrounding areas. As in Figure 5.12, the context can change the color perception.

11. Very few people see the world entirely in black and white. The more common condition is difficulty discriminating red from green.

Module 5.1 | End-of-Module Quiz

1. What term refers to the fact that rubbing your eyes makes you see something?

- **a.** Retinex theory
- **b.** Young-Helmholtz theory
- **c.** Law of specific nerve energies
- **d.** Monism

2. The fictional character Superman is said to have x-ray vision. What would happen if your eyes could send out x-rays?

- **a.** You could see through everything except lead.
- **b.** You could see through everything, even lead.
- **c.** You could see farther than usual.
- **d.** You would increase other people's cancer risk.

3. What is the route from retinal receptors to the brain?

- **a.** Receptors send axons directly to the brain.
- **b.** Receptors connect to bipolars, which connect to ganglion cells, which send axons to the brain.
- **c.** Receptors connect to ganglion cells, which connect to bipolars, which send axons to the brain.
- **d.** Receptors connect to amacrine cells, which send axons to the brain.

4. What axons form the optic nerve?

- **a.** Axons from the rods and cones
- **b.** Axons from the bipolar cells
- **c.** Axons from the ganglion cells
- **d.** Axons from all the rods, cones, bipolar cells, and ganglion cells

5. Why is vision most acute at the fovea?

- **a.** The fovea is closest to the pupil.
- **b.** The fovea has an equal ratio of cones to rods.
- **c.** Many receptors in the fovea converge their input onto each bipolar cell.
- **d.** Receptors in the fovea connect to midget ganglion cells.

6. Why does vision in the periphery have high sensitivity to faint light?

- **a.** Toward the periphery, the retina has more midget ganglion cells.
- **b.** Toward the periphery, the retina has more cones and fewer rods.
- **c.** Toward the periphery, the retina has more convergence of input.
- **d.** Toward the periphery, the light falls farther from the blind spot.

7. Why do some people have greater than average sensitivity to brief, faint, or rapidly changing visual stimuli?

- **a.** They do not have a blind spot in their retina.
- **b.** The blind spot in their retina is smaller than average.
- **c.** They have more axons from the retina to the brain.
- **d.** They have four types of cones instead of three.

8. Compared to many birds, what is true of human color vision, and why?

- **a.** Humans have better color vision, because we have three types of cone instead of one.
- **b.** Humans have better color vision, because we have three types of cone instead of two.
- **c.** Humans are color-vision deficient, because we do not see ultraviolet radiation.
- **d.** Humans are color-vision deficient, because we do not see infrared radiation.

9. Suppose you perceive something as red. According to the trichromatic theory, what is the explanation?

- **a.** Light from the object has excited your long-wavelength cones more strongly than your other cones.
- **b.** Light from the object has excited your short-wavelength cones more strongly than your other cones.
- **c.** Ganglion cells that increase response to red and decrease their response to green are firing strongly.
- **d.** The cortex compares activity over all parts of the retina and computes that one area is red.

10. An object that reflects all wavelengths equally would ordinarily appear gray, but it may appear yellow, blue, or any other color, depending on what?

- **a.** Brightness of the light
- **b.** Contrast with surrounding objects
- **c.** The culture in which you grew up
- **d.** The ratio of cones to rods in your retina

11. Color vision deficiency demonstrates which fundamental point about perception?

- **a.** Color is in the brain and not in the light itself.
- **b.** Each sensory system depends on a different part of the cerebral cortex.
- **c.** Color perception varies because of cultural influences.
- **d.** Fatiguing a receptor can lead to a negative afterimage.

Answers: 1c, 2d, 3b, 4c, 5d, 6c, 7c, 8c, 9a, 10b, 11a.

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Module 5.2

Visual Processing in the Brain

Learning Objectives

After studying this module, you should be able to:

5. Trace the route of visual information from the retina to the cerebral cortex.
6. Explain lateral inhibition in terms of the connections among neurons in the retina.
7. Define and give examples of receptive fields.
8. Describe research on how experiences alter development of the visual cortex.

We consider brain mechanisms of vision in detail, for two reasons. First, everything in psychology starts with sensations, and humans rely heavily on vision. Second, neuroscientists have investigated vision in more detail than any other brain activity. Examining the mechanisms of vision demonstrates the kind of explanation we would like to accomplish for other psychological processes.

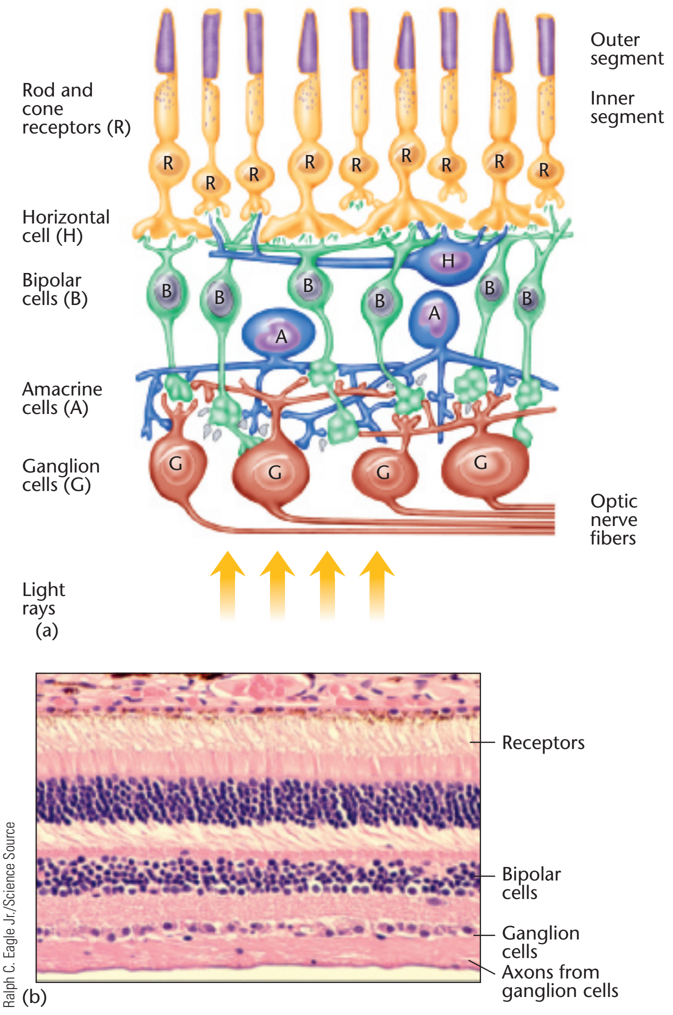
An Overview of the Mammalian Visual System

Let's begin with the anatomy of the mammalian visual system. The rods and cones of the retina make synapses with **horizontal cells** and bipolar cells (Figures 5.3 and 5.14). The horizontal cells make inhibitory contact onto bipolar cells, which in turn make synapses onto *amacrine cells* and ganglion cells. All these cells are within the eyeball.

The axons of the ganglion cells form the optic nerve, which leaves the retina and travels along the lower surface of the brain until the optic nerves from both eyes meet at the optic chiasm (Figure 5.15a). There, in humans, half the axons from each eye cross to the opposite side of the brain. As depicted in Figure 5.15b, information from the nasal half of each eye (the side closer to the nose) crosses to the contralateral hemisphere. Information from the temporal half (the side toward the temporal cortex) goes to the ipsilateral hemisphere. The percentage of crossover varies from one species to another depending on the location of the eyes. In species with eyes far to the sides of the head, such as rabbits and guinea pigs, most axons cross to the opposite side.

Figure 5.14 The vertebrate retina

The top of the figure is the back of the retina. The optic nerve fibers group together and exit through the back of the retina, in the blind spot of the eye.



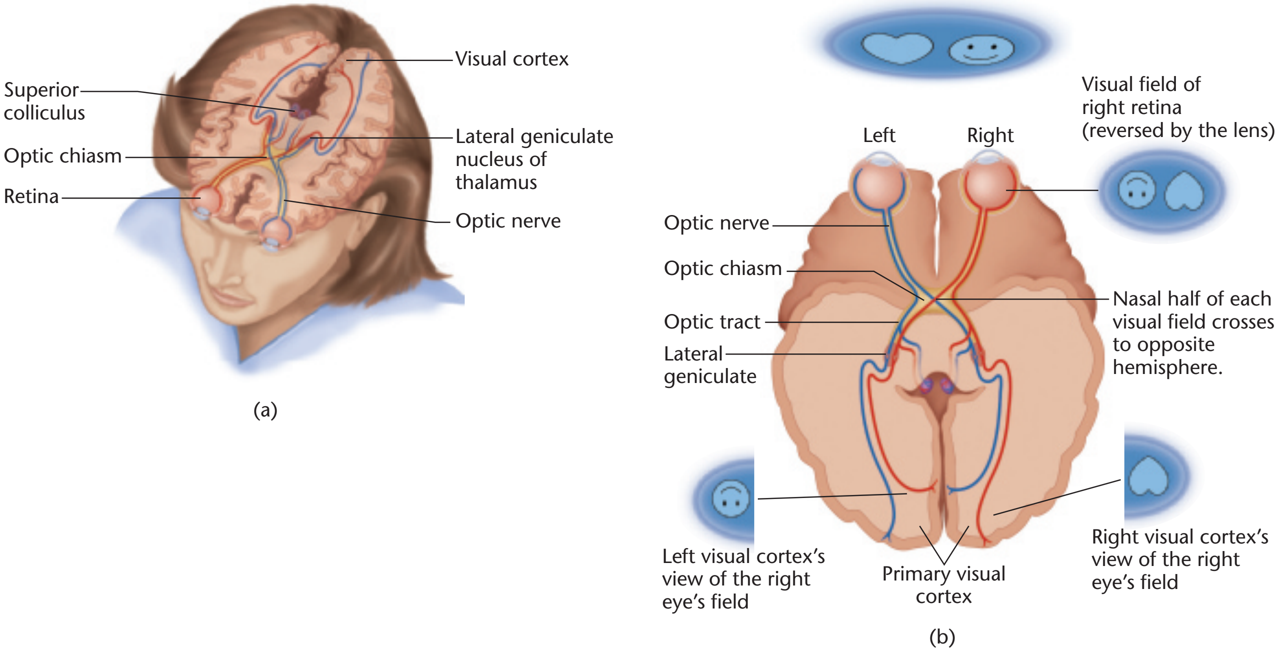
Ralph C. Eagle Jr./Science Source

(**Source:** Based on "Organization of the Primate Retina," by J. E. Dowling and B. B. Boycott, *Proceedings of the Royal Society of London*, B, 1966, 166, pp. 80–111. Used by permission of the Royal Society of London and John Dowling.)

Most of the optic nerve goes to the **lateral geniculate nucleus** of the thalamus. (The term *geniculate* comes from the Latin root *genu*, meaning "knee." To

Figure 5.15 Major connections in the visual system

(a) Part of the visual input goes to the thalamus and from there to the visual cortex. Another part goes to the superior colliculus. (b) Axons from the retina maintain their relationship to one another—their *retinotopic organization*—throughout their journey from the retina to the lateral geniculate to the cortex.


Superior colliculus
Optic chiasm
Retina
Visual cortex
Lateral geniculate nucleus of thalamus
Optic nerve
(a)
Left
Right
Visual field of right retina (reversed by the lens)
Optic nerve
Optic chiasm
Optic tract
Lateral geniculate
Nasal half of each visual field crosses to opposite hemisphere.
Left visual cortex's view of the right eye's field
Primary visual cortex
Right visual cortex's view of the right eye's field
(b)

genuflect is to bend the knee. The shape of the lateral geniculate must have looked like a knee to some early anatomist.) Other axons go from the eye to the superior colliculus (important for eye movements, among other functions) and to the part of the hypothalamus that controls the waking–sleeping schedule. The lateral geniculate sends input to other parts of the thalamus and to the visual cortex. Axons from the cortex go back to the thalamus to modify thalamic activity (Ling et al., 2015).

Stop & Check

12. Where does the optic nerve start and where does it end?

See page 173 for the answer.

Processing in the Retina

The human eye includes about a quarter of a billion receptors. From that, you need to extract the meaningful patterns. Let's explore one example in detail: lateral inhibition.

Lateral inhibition is the retina's way of sharpening contrasts to emphasize the borders of objects. Here is an analogy to demonstrate how it works: Suppose people stand in a line, each holding one cookie. Someone hands 5 extra cookies to the 5 people in the middle of the line, but then each of those 5 people has to throw away one of their own cookies, and one cookie from each of their neighbors. If you want as many cookies as possible, where is the best place to be? You don't want to be in the middle of the cookie-receiving group, because after gaining 5 you would have to throw away one of your own and lose one to each of your neighbors. But if you're either the first or fifth person to receive a cookie, you'll gain five and then throw away one and lose one to just one neighbor (a loss of 2). The worst place to be is right before or after the group receiving cookies, because you would lose the cookie you already had. The result is a sharp contrast at the border between those receiving cookies and those not.

The analogy may sound silly—okay, it *is* silly—but it illustrates what happens in the retina. The receptors send messages to excite nearby bipolar cells (like giving them cookies), and they also send messages to horizontal cells that slightly inhibit those bipolar cells and the neighbors to their sides. The net result heightens the contrast between an illuminated area and its darker surround.

Actually, light striking the rods and cones *decreases* their spontaneous output, and the receptors make *inhibitory* synapses onto the bipolar cells. Therefore, light on the rods or cones decreases their inhibitory output. Decreased inhibition means net excitation, so to avoid double negatives, let's think of the receptors' output as excitation of the bipolar cells.

In the fovea, each cone attaches to just one bipolar cell. In the following diagram, green arrows represent

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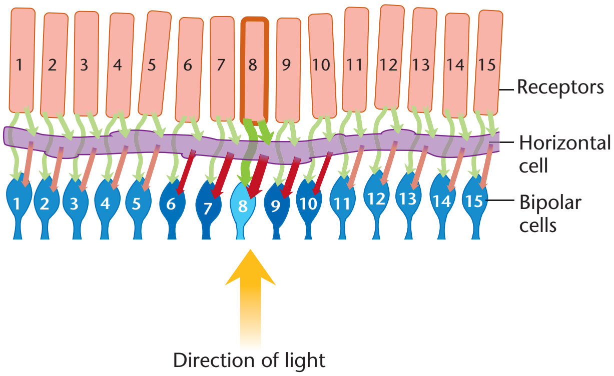
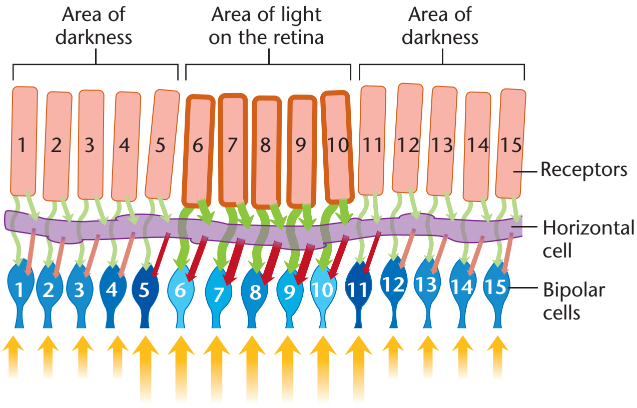
excitation, and the width of an arrow indicates the amount of excitation. Receptor 8, which is highlighted, excites bipolar cell 8. It also excites a horizontal cell that inhibits bipolar cells, especially the closest ones, as depicted by red arrows. Bipolar cell 8 has net excitation, because the excitatory synapse outweighs the effect of the horizontal cell's inhibition. (It's like gaining cookies and then losing a smaller number.) The bipolar cells to the sides (laterally) get no excitation but some inhibition. In this diagram, the thickness of the arrow indicates the amount of excitation or inhibition. Lighter blue indicates more net excitation in a bipolar cell.



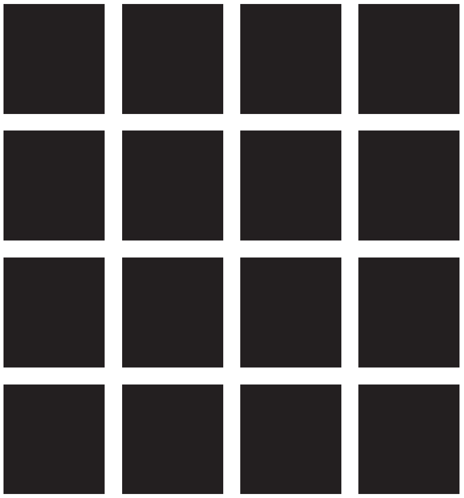
Now imagine that light excites receptors 6 through 10. These receptors excite bipolar cells 6 through 10 and the horizontal cell. Bipolar cells 7, 8, and 9 are inhibited by input on both sides, but bipolar cells 6 and 10 are inhibited from only one side, and therefore 6 and 10 respond the most. Bipolar cells 5 and 11 receive no excitation, but the horizontal cell inhibits them. They respond the least.



These results illustrate **lateral inhibition**, reduced activity in a neuron because of activity in neighboring neurons (Hartline, 1949). Lateral inhibition heightens contrast. Lateral inhibition is important for many functions. In olfaction, a strong stimulus uses lateral inhibition to suppress the response to one that follows slightly after it (Whitesell et al., 2013). In touch, stimulating a spot on the skin weakens the response to stimulation of a neighboring spot, again by lateral inhibition (Severens et al., 2010). In hearing, lateral inhibition helps us hear speech amid irrelevant noise (Bashford et al., 2013).

Figure 5.16 An illustration of lateral inhibition

Do you see dark diamonds at the "crossroads"?



Stop & Check

13. When light strikes a receptor, does the receptor excite or inhibit the bipolar cells? What effect does it have on horizontal cells? What effect does the horizontal cell have on bipolar cells?
14. If light strikes only one receptor, what is the net effect (excitatory or inhibitory) on the nearest bipolar cell that is directly connected to that receptor? What is the effect on bipolar cells to the sides? What causes that effect?
15. In Figure 5.16, you may see grayish diamonds at the crossroads among the black squares. Explain why.

See page 173 for the answer.

Further Processing

Each cell in the visual system of the brain has a **receptive field**, an area in visual space from which light excites or inhibits the cell. The receptive field of a rod or cone is the point in space from which light strikes the cell. Other visual cells derive their receptive fields from the connections they receive. For analogy, suppose you keep track of events on a city block. We'll call that your receptive field. Other people keep track of events on other blocks. Everyone on the street reports to a supervisor, whose receptive field is the whole street, the combined area of input. All the street supervisors report to the neighborhood manager, whose receptive field is the whole neighborhood. And so on.

The same idea applies to vision. Rods and cones with tiny receptive fields connect to a bipolar cell, with a receptive field that combines those of all cells connected to it,

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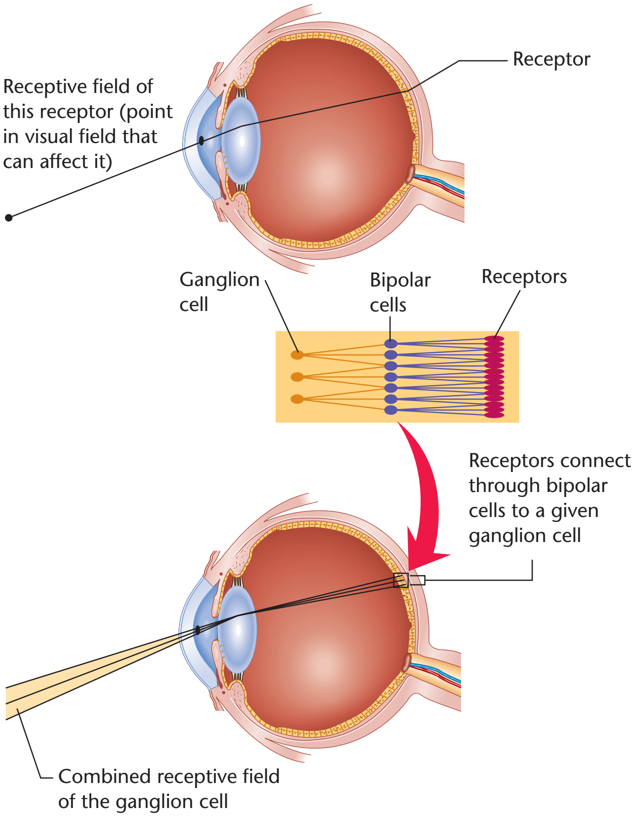
Figure 5.17 Receptive fields

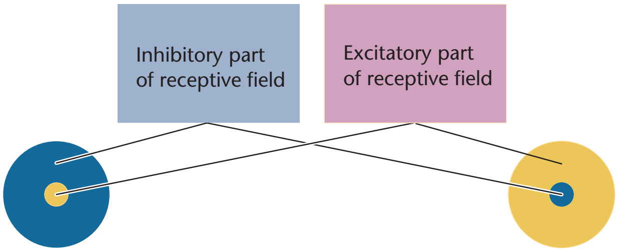
The receptive field of any neuron in the visual system is the area of the visual field that excites or inhibits it. Receptors have tiny receptive fields and later cells have progressively larger receptive fields.


Receptive field of this receptor (point in visual field that can affect it)
Receptor
Ganglion cell
Bipolar cells
Receptors
Receptors connect through bipolar cells to a given ganglion cell
Combined receptive field of the ganglion cell

both excitatory and inhibitory. Bipolar cells report to a ganglion cell, which therefore has a larger receptive field, as illustrated in Figure 5.17. The receptive fields of ganglion cells converge at the next level, and so on.

To find a cell's receptive field, an investigator records from the cell while shining light in various locations. If light on a particular spot excites or inhibits the neuron, then that location is part of the neuron's excitatory or inhibitory receptive field.

The receptive fields of ganglion cells have varying properties. In the simplest case, a ganglion cell's receptive field has a circular center and an antagonistic doughnut-shaped surround. The receptive field might be excited by light in the center and inhibited by light in the surround, or the opposite.

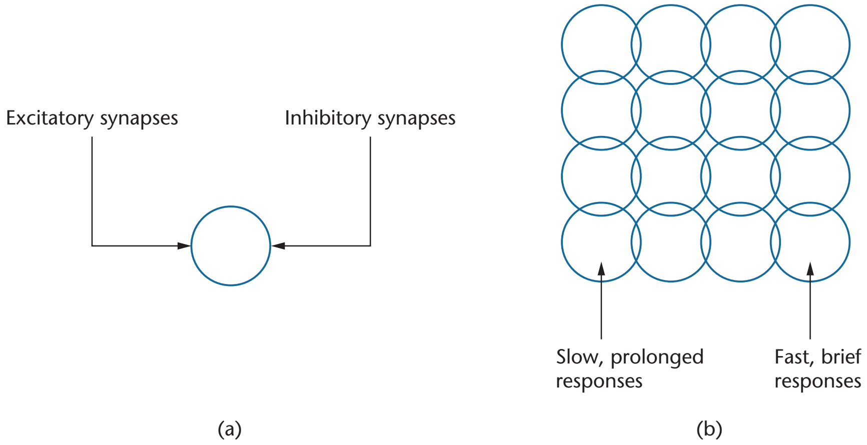

Inhibitory part of receptive field
Excitatory part of receptive field

Ganglion cells are spaced out evenly across the retina, usually alternating excitatory-inhibitory (Roy et al., 2021). Some ganglion cells respond only briefly to changing stimuli. Some ganglion cells respond only to a stimulus moving in a particular direction. Figure 5.18 illustrates two ways to make a cell direction-selective (Lien and Scanziani, 2018; Rossi et al., 2020).

Primate ganglion cells fall into three categories: parvocellular, magnocellular, and koniocellular (Edwards et al., 2021;

Figure 5.18 Two ways to make a visual neuron direction-selective

Suppose a neuron receives input from the cells shown in parts A or B. The cell in part A would respond briefly to a stimulus going left to right, before being inhibited. A stimulus going right to left would be inhibited before the excitation had a chance to produce a response. In B, a stimulus moving left to right would produce gradual summation. For a stimulus moving right to left, the excitation would decay before the stimulus reached the left side.


Excitatory synapses
Inhibitory synapses
Slow, prolonged responses
Fast, brief responses
(a)
(b)

(**Source:** Lien and Scanziani, 2018; Rossi et al., 2020)

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Table 5.2 | Three Kinds of Primate Ganglion Cells

	Parvocellular neurons	Magnocellular neurons	Koniocellular neurons
Cell bodies	Small	Large	Small
Receptive fields	Small	Large	Mostly small, but variable
Retinal location	In and near fovea	Throughout the retina	Throughout the retina
Color sensitive?	Yes	No	Some are
Respond to	Detailed shape	Movement and broad outlines of shape	Varied

Nassi and Callaway, 2009). The most numerous type, **parvocellular neurons**, have small cell bodies and small receptive fields, mostly in or near the fovea. (Parvocellular means "small celled," from the Latin root *parv*, meaning "small.") **Magnocellular neurons**, with larger cell bodies and receptive fields, are distributed evenly throughout the retina. (Magnocellular means "large celled," from the Latin root *magn*, meaning "large," as in the word *magnify*.) The **koniocellular neurons** have small cell bodies, like the parvocellular neurons, but they occur throughout the retina. (Koniocellular means "dust celled," from the Greek root meaning "dust." They got this name because of their granular appearance.)

The parvocellular neurons, with their small receptive fields connected to cones in the fovea, detect visual details and colors. The magnocellular neurons, with larger receptive fields, respond to movement and overall patterns, but not color or fine details. A large receptive field is helpful for detecting movement. Koniocellular neurons have a variety of functions (Hendry and Reid, 2000). The diversity of ganglion cells indicates that the visual system analyzes information in many ways from the start. Table 5.2 contrasts the three kinds of ganglion cells.

Stop & Check

16. As we progress from bipolar cells to ganglion cells to later cells in the visual system, are receptive fields ordinarily larger, smaller, or the same size? Why?
17. How do parvocellular and magnocellular systems differ?

See page 173 for the answer.

The Primary Visual Cortex

Information goes from the ganglion cells to the lateral geniculate nucleus of the thalamus and then to the **primary visual cortex** in the occipital cortex, also known as area **V1** or the *striate cortex* because of its striped appearance. Activity from V1 projects to the frontal cortex, which within 100–200 milliseconds sends information back to modify the activity in V1 and other visual areas. The activity in V1 corresponds to your conscious visual experience (Stoerig, 2001). If you close your eyes and imagine seeing something, activity increases in area V1 (Kosslyn and Thompson, 2003; Stokes et al., 2009). People with damage in and around area V1 report no conscious vision, no visual imagery, and no visual dreams (Hurovitz et al., 1999).

Try this: Imagine a familiar scene, such as the home you grew up in. When people imagine a visual scene, the vividness of their images varies more than you might guess. About 1 to 3 percent of people have no visual imagery at all, other than maybe in a dream now and then. They might also have little or no auditory imagery or other types of sensory imagination. People with this condition, called **aphantasia**, tend to be attracted toward math and science. At the opposite extreme, people with **hyperphantasia** can imagine a visual scene almost as vividly as actually seeing it. Hyperphantasia is more common among women than men, and it tends to be associated with artistic and other creative occupations (Zeman, 2021; Zeman et al., 2020). Visual imagery differs from actual vision in this regard: When you see something, activity starts in area V1 and spreads. When you imagine a visual scene, the activity starts in the memory and language areas of the cortex, and then spreads gradually to V1.

Some people with damage to area V1 display a surprising phenomenon called **blindsight**, the ability to respond to visual information without perceiving it consciously. Within the damaged part of their visual field, they cannot even distinguish between bright sunshine and utter darkness. Nevertheless, they might be able to point accurately to something in the area where they cannot see, or move their eyes toward it, while insisting that they are "just guessing" (Bridgeman and Staggs, 1982; Weiskrantz et al., 1974). Some patients with blindsight can reach for an object they cannot see, avoiding obstacles in the way (Striemer et al., 2009). Some can identify an object's shape, color, or direction of movement, or copy the emotional expression of a face, still insisting that they are just guessing (Gonzalez Andino et al., 2009; Radoeva et al., 2008; Tamietto et al., 2009). Many patients respond in one of these ways and not the others, because of differences in which connections were damaged. Most say they are completely unaware of the visual input, but some say they were aware of "something," without being able to specify what it was.

One proposed explanation for blindsight is that small islands of healthy tissue may survive in an otherwise damaged area (Fendrich et al., 1992; Radoeva et al., 2008). Another explanation is that some of the input from the eyes goes to areas other than V1 (Ajina et al., 2020; Beltramo and Scanziani, 2019; Schmid et al., 2013).

In one study, every patient with blindsight had intact connections from the visual area of the thalamus to the temporal cortex (Ajina et al., 2015). In any case, the conclusion remains that V1 and surrounding areas are essential for conscious vision.

Even if your brain is intact, you could experience something like blindsight under certain circumstances. Researchers set up an apparatus so that people saw a face or a tool for three-tenths of a second in just one eye, while the other eye was viewing a display that changed 10 times a second. In this procedure, known as *continuous flash suppression*, the rapidly changing stimuli captures attention, and the viewer is not conscious of the steady picture. However, even though people insist they did not see a face or tool, when they were asked to guess where it was (upper left, upper right, lower left, or lower right), they were correct almost half the time, as opposed to the one-fourth we could expect by chance (Hesselmann et al., 2011).

Stop & Check

18. How is visual imagery similar to seeing something, and how is it different?
19. What does blindsight tell us about conscious vision?

See page 173 for the answer.

Simple and Complex Receptive Fields

In the 1950s, David Hubel and Torsten Wiesel (1959) inserted thin electrodes to record activity from cells in cats' and monkeys' occipital cortex while they presented visual patterns to the retina. At first, they presented dots of light, using a slide projector and a screen, but they found little response by cortical cells. Then they noticed a big response while they were moving a slide into place. They realized that the cell was responding to the edge of the slide. The cell had a bar-shaped receptive field, rather than a circular receptive field like cells in the retina and lateral geniculate (Hubel and Wiesel, 1998).

Hubel and Wiesel distinguished several types of cells in the visual cortex. Figure 5.19 illustrates the receptive field of a **simple cell**. A simple cell has a receptive field with fixed excitatory and inhibitory zones. Light in the excitatory zone increases responses and light in the inhibitory zone decreases it. In Figure 5.19, the receptive field is a vertical bar. Tilting the bar or moving it to a different place reduces the response. Most simple cells have bar-shaped or edge-shaped receptive fields in horizontal or vertical orientations. That tendency makes sense, considering the importance of horizontal and vertical objects in our world (Coppola et al., 1998).

Complex cells, located in areas V1 and V2, also respond to bars and edges, but they respond equally anywhere within a large receptive field (Figure 5.20). Most complex cells respond mostly to a stimulus moving in a particular direction—for example, a vertical bar moving left to right. The best way to classify a cell as simple or complex is to present a stimulus in several locations. A cell that responds to a stimulus in only one location is a simple cell. One that responds anywhere within a larger area is a complex cell. An **end-stopped** or **hypercomplex** cell resembles a complex cell except that it has a strong inhibitory area at one end of its bar-shaped receptive field (Figure 5.21). Table 5.3 summarizes the properties of simple, complex, and end-stopped cells.

Colin Blakemore/Oxford University

David Hubel (1926–2013)

Brain science is difficult and tricky, for some reason; consequently one should not believe a result (one's own or anyone else's) until it is proven backwards and forwards or fits into a framework so highly evolved and systematic that it couldn't be wrong. (Hubel, personal communication)

Jose Huesca/European Pressphoto Agency/Madrid/Spain/Newscom

Torsten Wiesel (b. 1924)

Neural connections can be modulated by environmental influences during a critical period of postnatal development. . . . Such sensitivity of the nervous system to the effects of experience may represent the fundamental mechanism by which the organism adapts to its environment during the period of growth and development. (Wiesel, 1982, p. 591)

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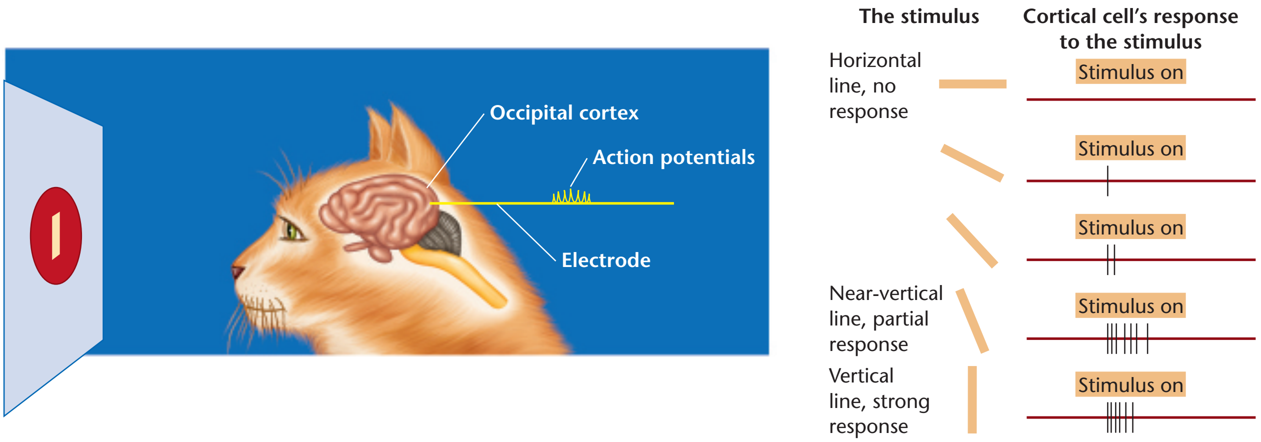
Figure 5.19 Responses of a cat's simple cell to a bar of light

This cell responds best to a vertical line in a particular location. Other simple cells respond to lines at other orientations.


The stimulus
Cortical cell's response to the stimulus
Occipital cortex
Action potentials
Electrode
Horizontal line, no response
Stimulus on
Stimulus on
Stimulus on
Near-vertical line, partial response
Stimulus on
Vertical line, strong response
Stimulus on

(**Source:** Right, from D. H. Hubel and T. N. Wiesel, "Receptive fields of single neurons in the cat's striate cortex," *Journal of Physiology, 148*, 1959, 574–591. Copyright © 1959 Cambridge University Press. Reprinted by permission.)

Figure 5.20 The receptive field of a complex cell

Like a simple cell, its response depends on a bar of light's angle of orientation. However, a complex cell responds the same for a bar in any location within a large receptive field.

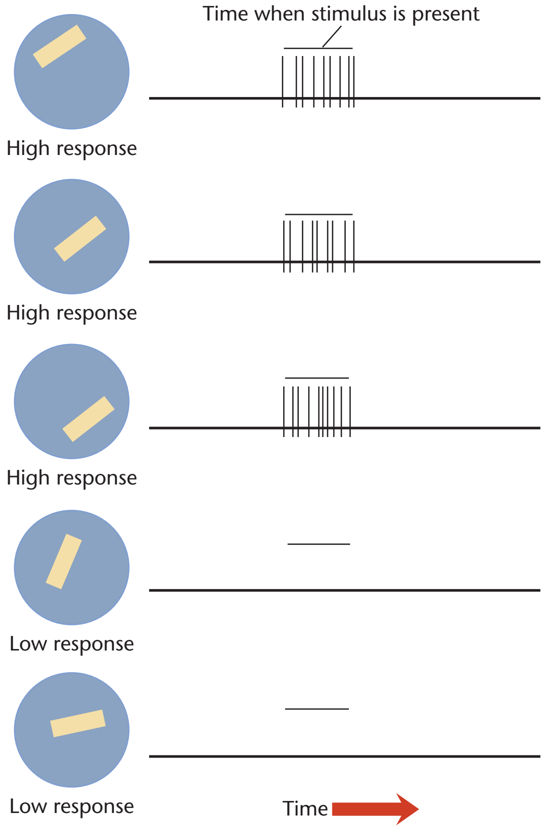
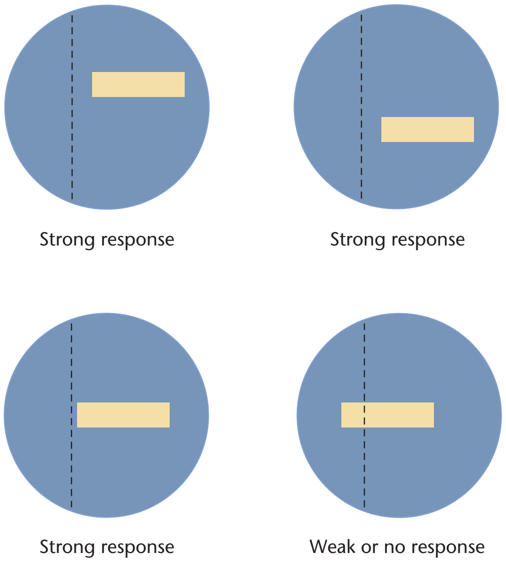

Time when stimulus is present
High response
High response
High response
Low response
Low response
Time

Figure 5.21 The receptive field of an end-stopped cell

The cell responds to a bar in a particular orientation (in this case horizontal) anywhere in its receptive field, provided the bar does not extend into a strongly inhibitory area.


Strong response
Strong response
Strong response
Weak or no response

Later researchers found that a cortical cell that responds well to a single bar or line

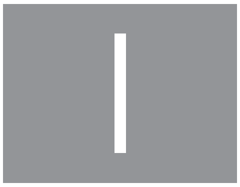


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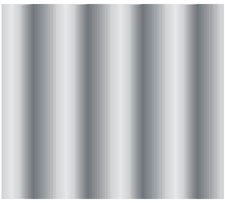
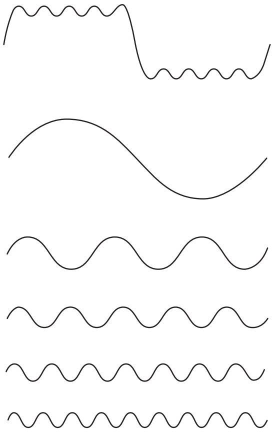
Table 5.3 | Cells in the Primary Visual Cortex

	Simple cells	Complex cells	End-stopped cells
Location	V1	V1 and V2	V1 and V2
Binocular input?	Yes	Yes	Yes
Size of receptive field	Smallest	Medium	Largest
Shape of receptive field	Bar- or edge-shaped, with fixed excitatory and inhibitory zones	Bar- or edge-shaped, but responding equally throughout a large receptive field	Same as complex cell, but with a strong inhibitory zone at one end

responds even more strongly to a sine wave grating of bars or lines:



Many cortical neurons respond best to a particular spatial frequency of lines and hardly at all to other frequencies (DeValois et al., 1982). How do we translate a series of spatial frequencies into perception? From a mathematical standpoint, sine wave frequencies are easy to work with. A branch of mathematics called Fourier analysis demonstrates that a combination of sine waves can produce an unlimited variety of other patterns. For example, the graph at the top of the following display is the sum of the five sine waves below it:



Thus, a series of spatial frequency detectors, some sensitive to horizontal patterns and others to vertical patterns, could represent any possible display. Still, we perceive the world as objects, not sine waves. How the brain codes vision does not match what we see in any very simple way.

Stop & Check

20. How could a researcher determine whether a given neuron in the visual cortex is simple or complex?

See page 173 for the answer.

Are Visual Cortex Cells Feature Detectors?

Given that neurons in area V1 respond strongly to particular patterns, we might suppose that the activity of such a cell represents the perception of that pattern, such as lines or bars. If so, such cells would be **feature detectors**—neurons whose responses indicate the presence of a particular feature.

Supporting the idea of feature detectors is the fact that prolonged exposure to a given visual feature decreases sensitivity to that feature, as if it fatigued the relevant detectors. For example, if you stare at a waterfall for a minute or more and then look away, the rocks and trees next to the waterfall appear to flow upward. This *waterfall illusion* suggests that you have fatigued the neurons that detect downward motion, leaving unopposed the detectors for the opposite motion.

Long ago, Gestalt psychologists rejected the idea that feature detectors tell the whole story about our perceptions. For example, if you examine Figure 5.22, you might at first see nothing. Then suddenly you exclaim, "Oh, that's a face! [pause] And another face!" Looking at these displays (known as Mooney faces) requires interpretation and reorganization of the material, not just passively stimulating feature detectors. When you start seeing the displays as faces, the pattern of responses in your visual cortex suddenly changes (Hsieh et al., 2010). It is a top-down process in which other brain areas interpret the visual stimulus and send messages back to reorganize V1 activity. Similarly, when you see an optical illusion, it is due to feedback from other cortical areas that changes responses in V1 (Sperandie et al., 2012; Wokke et al., 2013). In a sense, the brain is constantly forming hypotheses or expectations about the world, and then modifying them based on "prediction errors" when it compares the expectations to sensory input (Walsh et al., 2020).

Stop & Check

21. What is a feature detector?
22. What evidence indicates that feature detectors do not explain all of perception?

See page 174 for the answer.

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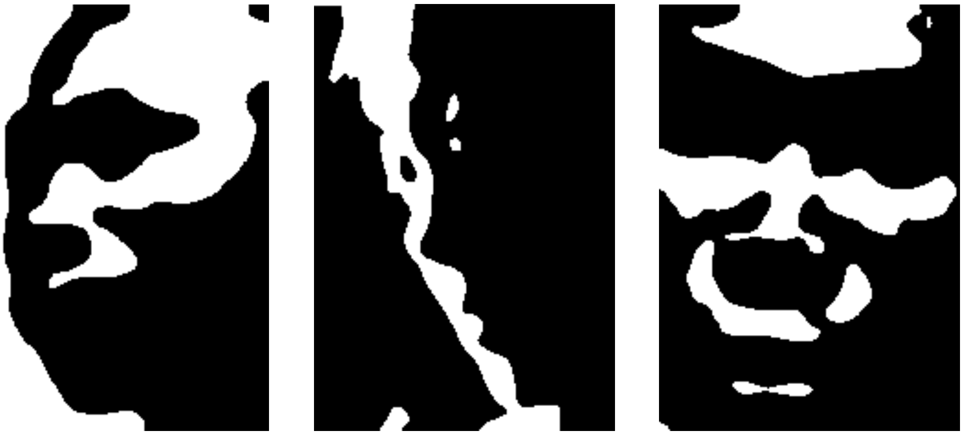
Figure 5.22 Mooney faces

At first glance, you may see only meaningless blobs. With some time and effort, you may get an "Aha" experience and suddenly see them as faces.



Aaron Schurger/Dept. of Psychology, Princeton University

Development of the Visual Cortex

Suppose you had lived all your life in the dark. Then, for the first time, you came out into the light and looked around. Would you understand anything?

Unless you were born blind, you did have this experience—on the day you were born! At first, presumably you had no idea what you were seeing. Within months, however, you began to recognize faces and crawl toward your favorite toys. How did you learn to make sense of what you saw? The young of mammals such as horses have to make sense of vision quickly, as they start walking and following their mother shortly after birth.

In a newborn mammal, many properties of the visual system develop before birth (Lein and Shatz, 2001; Shatz, 1996). Waves of spontaneous activity sweep over the developing retina, synchronizing the activity of neighboring receptors and enabling appropriate combinations of receptors to establish connections with cells in the brain (Ackman et al., 2012; Zhang et al., 2012). A study of people who were born without eyes found that the connections from the primary visual cortex to its main targets were more or less normal (Bock et al., 2015). Evidently, certain axon paths develop automatically, at least at first. Nevertheless, visual experience after birth is necessary for maintaining and modifying the connections.

Deprived Experience in One Eye

What would happen if a young animal could see with one eye but not the other? When a kitten opens its eyes at about age 9 days, each neuron responds to areas in the two retinas that focus on approximately the same point in space—a process necessary for binocular vision. However, innate mechanisms cannot make the connections exactly right because the exact distance between the eyes varies from one kitten to another, and the distance changes over age. Therefore, experience is necessary for fine-tuning.

If an experimenter sutures one eyelid shut for a kitten's first 4 to 6 weeks of life, synapses in the visual cortex gradually become unresponsive to input from the deprived eye (Rittenhouse et al., 1999). After the deprived eye is opened, the kitten does not respond to it. A similar period of deprivation in older animals weakens the response to the deprived eye, but not as strongly as it does in young ones (Wiesel, 1982; Wiesel and Hubel, 1963). After an eye deprived of vision in adults is reopened, cells gradually return to their previous levels of responsiveness (Rose et al., 2016).

Deprived Experience in Both Eyes

If *both* eyes stayed shut for the first few weeks, what would you expect? You might guess that the kitten would become insensitive to both eyes, but it does not. When just one eye is open, the synapses from the open eye release a chemical that inhibits the synapses from the closed eye (Maffei et al., 2006; Yasuda et al., 2021). If neither eye is active, no axon outcompetes any other. For at least 3 weeks, the kitten's cortex remains responsive to visual input, although most cells become responsive to just one eye or the other and not both (Wiesel, 1982). If the eyes remain shut still longer, the cortical responses start to become sluggish and lose their well-defined receptive fields (Crair et al., 1998). Eventually, the visual cortex may start responding to auditory or touch stimuli instead.

For each aspect of visual experience, researchers identify a **sensitive period**, when experiences have a particularly strong and enduring influence (T. L. Lewis and Maurer, 2005; Tagawa et al., 2005). The sensitive period depends on inhibitory neurons. A study with mice found that transplanting inhibitory neurons from an

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infant into an older mouse could induce a new period of heightened susceptibility to experience (Southwell et al., 2010). However, even long after the sensitive period, a prolonged experience—such as a full week without visual stimulation to one eye—produces a smaller but measurable effect on the visual cortex (Sato and Stryker, 2008). Cortical plasticity is greatest in early life, but it never ends.

Stop & Check

23. What is the effect of closing one eye early in a kitten's life? What is the effect of closing both eyes?

See page 174 for the answer.

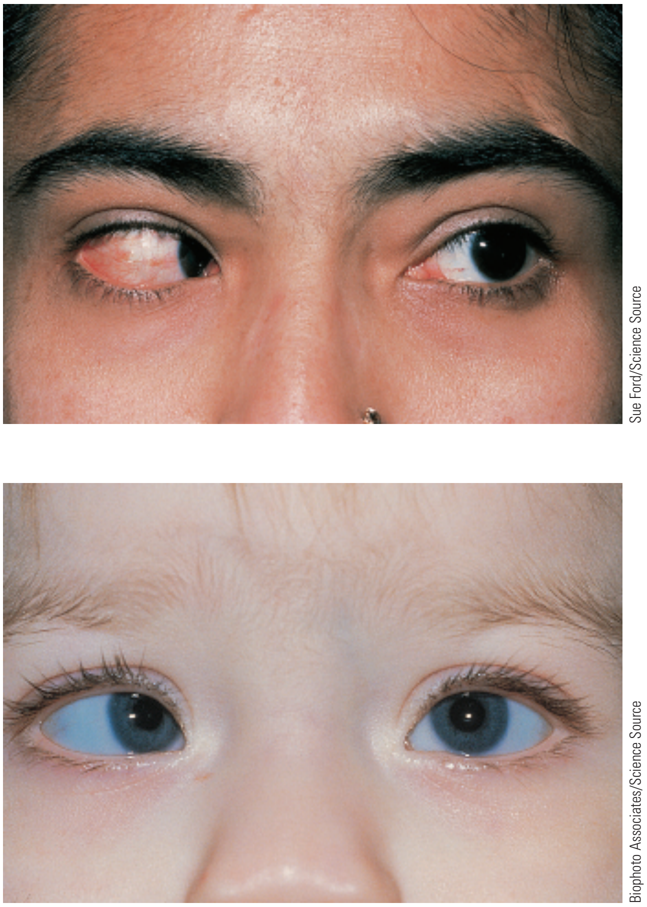
Uncorrelated Stimulation in the Two Eyes

Stereoscopic depth perception requires the brain to detect **retinal disparity**, the discrepancy between what the left and right eyes see. Most neurons in the human visual cortex contribute to this process. During early development, each neuron in the visual cortex receives many inputs from both eyes, but it uses inhibitory synapses to suppress unmatching inputs. The result is to make the neuron responsive to corresponding areas of the left and right eyes—areas that see the same thing at the same time (Yaeger et al., 2019). A neuron that cannot find matching input from the two eyes will become responsive to just one eye or the other (Tan et al., 2020).

Abnormal experience disrupts this process. Imagine a kitten with weak or damaged eye muscles so that its eyes do not point in the same direction. Both eyes are active, but no cortical neuron consistently receives matching messages from the two eyes. Therefore, almost every neuron in the visual cortex becomes responsive to just one eye or the other (Blake and Hirsch, 1975; Hubel and Wiesel, 1965). The behavioral result is poor depth perception.

A similar phenomenon occurs in humans. Certain children are born with **strabismus** (or strabismic amblyopia), also known as "lazy eye," a condition in which the eyes do not point in the same direction. Most of these children attend to one eye and not the other. A common treatment has been to put a patch over the active eye, forcing attention to the other one. That procedure increases attention to the ignored eye, especially if it begins early (T. L. Lewis and Maurer, 2005), but many children refuse to wear an eye patch for long enough. In any case, the procedure does not prompt the child to use both eyes at the same time.

One promising therapy is to ask a child to play three-dimensional action video games that require attention to both eyes (Li et al., 2014). Another is for the child to wear a head-mounted device that controls the input so that each eye has a clear view of only part of each scene. To make sense of the world, the child has to integrate what one eye sees with what the other one sees (Bao et al., 2018).



Sue Ford/Science Source

Biophoto Associates/Science Source

Two examples of strabismus, or "lazy eye."

Stop & Check

24. Why does childhood strabismus impair binocular depth perception?

See page 174 for the answer.

Early Exposure to a Limited Array of Patterns

If a kitten spends its entire early sensitive period wearing goggles with horizontal lines painted on them (Figure 5.23), nearly all its visual cortex cells become responsive only to horizontal lines (Stryker and Sherk, 1975; Stryker et al., 1978). Even after months of later normal experience, the cat does not respond to vertical lines (D. E. Mitchell, 1980).

What happens if human infants are exposed mainly to vertical or horizontal lines instead of both equally? They become more sensitive to the kind of line they have seen. "Wait!" you scream. How could such a bizarre thing happen? No parents would let an experimenter subject

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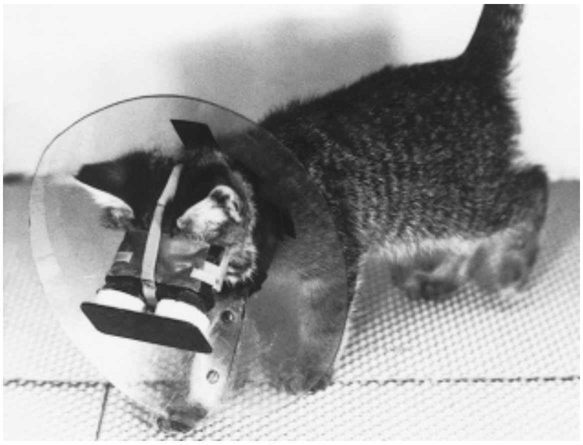
Figure 5.23 Procedure for restricting a kitten's visual experience

For a few hours a day, the kitten wears goggles that show just one stimulus, such as horizontal stripes or diagonal stripes. For the rest of the day, the kitten stays with its mother in a dark room without the mask.



(**Source:** Photo courtesy of Helmut V. B. Hirsch)

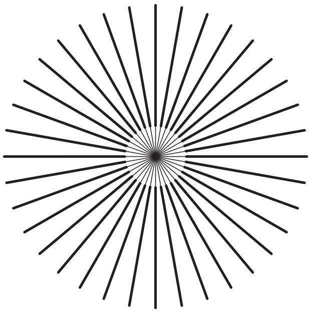
their child to such a procedure, and it never happens in nature. Right?

Wrong. In fact, it may have happened to you! About 70 percent of all infants have **astigmatism**, a blurring of vision for lines in one direction (e.g., horizontal, vertical, or one of the diagonals), caused by an asymmetric curvature of the eyes. Normal growth reduces the prevalence of astigmatism to about 10 percent in 4-year-old children.

You can informally test yourself for astigmatism with Figure 5.24. Do the lines in one direction look darker than another? If so, rotate the page to demonstrate that the darkness is in you, not in the lines themselves. The appearance of the lines depends on their position. If you wear corrective lenses, try this demonstration with and without them. If you see a difference in the lines only without your lenses, then the lenses have corrected your astigmatism.

Figure 5.24 An informal test for astigmatism

Do the lines in one direction look darker or sharper than the other lines do? If so, notice what happens when you rotate the page. If you wear corrective lenses, try this demonstration both with and without your lenses.



Impaired Infant Vision and Long-Term Consequences

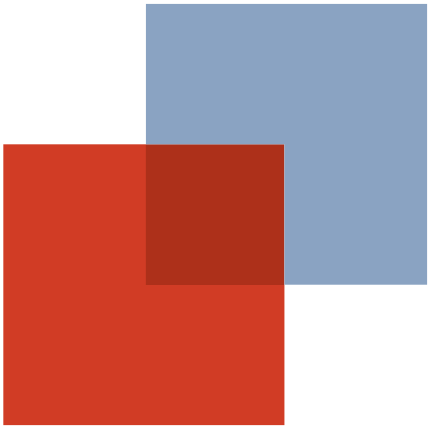
At the start of this section, we raised the question of what you would see if you lived all your life in the dark and then suddenly could see. In some countries, a newborn with dense cataracts (cloudy spots on the lenses that prevent perception of anything other than bright versus dark) may have to wait years for surgery to enable vision. When the cataracts are finally removed, researchers can examine what happened to vision after years of almost total deprivation.

At first, these children have only a limited understanding of what they see. In one study, children looked at a picture of a toy block, and another picture with two blocks. The task was to point to the block in the second picture that matched the first. Children did well on this task, indicating that they could see. However, when the task was to feel a block and point to which of two choices was the picture of that block, the children's performance was only a little better than chance. They could see the pictures, but they didn't understand them. A week later, without any special training, they improved on this task (Held et al., 2011). Within weeks they started recognizing faces. With much practice, they began to develop hand-eye coordination. Seeing well enough to ride a bicycle took a year and a half (Chatterjee, 2015; Gandhi et al., 2014). Some aspects of vision, such as motion perception and depth perception, never reached normal levels (Dormal et al., 2012; Ellemberg et al., 2002). A study of another group of children who had binocular cataracts surgically repaired at ages 6 to 11 reported much variation in their development. Some learned to find their way around a room visually, and some did not. All had trouble inferring three-dimensional structures from two-dimensional drawings or photographs (McKyton et al., 2015).

One man had normal vision in early childhood until age 3½, when a chemical explosion destroyed one eye and damaged the cornea of his other eye so badly that he could see nothing more than light vs. dark. By adulthood, he had no visual memories and no visual imagery. At age 43, a corneal transplant enabled him to recover vision. Immediately he could see colors, and soon he could identify simple shapes. Eventually he learned to recognize common household objects, but unlike most people who identify objects immediately, he had to think about it carefully (Fine et al., 2003). Even 10 years later, he could not identify whether a face was male or female, happy or sad (Huber et al., 2015). When viewing something like Figure 5.25, he reported seeing three objects,

Figure 5.25 How many squares?

Most people immediately see two squares, one overlapping the other. A man who lost vision from age 3½ until 43 sees this display as three objects.



instead of a partly transparent object overlapping a second one (Fine et al., 2003). While he was blind, he had learned to ski by following verbal directions and memorizing hills. When he tried skiing with his eyes open, the result was frightening. Two years later he could use vision to estimate the steepness of a hill, and he was willing to open his eyes while skiing, but only on relatively easy slopes. On the most difficult hills, he insisted on closing his eyes! Evidently, the visual understanding that most of us take for granted depends on practice early in life.

Stop & Check

25. What causes astigmatism, and how does it change vision?
26. If an infant is born with dense cataracts on both eyes and they are surgically removed years later, how well does the child see?

See page 174 for the answer.

Module 5.2 | In Closing

Understanding Vision by Understanding the Wiring Diagram

Your eyes are bombarded with a complex pattern of light emanating from every source in front of you. Out of all this, your brain needs to extract the most useful information. The nervous system from the start identifies the borders between one object and another by lateral inhibition. It identifies lines and their locations by simple and complex cells in the primary visual cortex. Researchers have gone a long way toward mapping out the excitatory and inhibitory connections that make these cells possible. The visual experiences you have at any moment are the result of an awe-inspiring complexity of connections and interactions among a huge number of neurons. Understanding what you see is also the product of years of experience.

Summary

1. The optic nerves of the two eyes join at the optic chiasm, where half of the axons from each eye cross to the opposite side of the brain. Most of the axons then travel to the lateral geniculate nucleus of the thalamus, which communicates with the visual cortex. **161**
2. Lateral inhibition is a mechanism that enhances the contrast at light–dark borders. **162**
3. Lateral inhibition in the vertebrate retina occurs because receptors stimulate the wide horizontal cells that inhibit bipolar cells to the sides of the stimulated area. **163**
4. A receptive field is an area of the visual field that excites or inhibits a visual neuron. The neuron's response may depend on the light's location, wavelength, or movement. **163**
5. In the mammalian vertebrate visual system, the parvocellular system is specialized for perception of color and fine details. The magnocellular system is specialized for perception of movement and overall patterns. **165**
6. People vary in their visual imagery from extremely vivid to none at all. Visual imagery starts with activity in the language or memory areas and spreads to gradually increasing activity in the visual cortex. **165**
7. After damage to area V1, people report no vision, even in dreams. However, some kinds of response (blindsight) can occur after damage to V1 despite the lack of conscious perception. **165**
8. Within the visual cortex, simple cells have fixed excitatory and inhibitory fields. Complex cells respond to a light pattern of a particular shape regardless of its exact location. **166**

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9. Understanding what you see requires much more than just adding up points and lines. Vision is an active interpretation based partly on expectations. **168**
10. Cells of the visual cortex develop nearly normal properties early in life. However, abnormal visual experience can change the properties of visual cells, especially if the experience occurs early in life. **169**
11. Cortical neurons become unresponsive to axons from an inactive eye because of competition with the active eye. If both eyes are closed, each cortical cell remains somewhat responsive, although that response becomes sluggish and less selective. **169**
12. Developing good stereoscopic depth perception requires early experience at seeing the same thing with corresponding portions of the two eyes. Otherwise, a neuron in the visual cortex becomes responsive to input from just one eye. **170**
13. If a kitten sees only horizontal or vertical lines during its sensitive period, most of the neurons in its visual cortex become responsive to such lines only. For the same reason, a child with astigmatism may have decreased responsiveness to one kind of line or another. **170**
14. Some people have cataracts removed after years of cloudy vision. Their vision, useless at first, improves with practice but remains imperfect. **171**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

aphantasia **165**
astigmatism **171**
blindsight **165**
complex cells **166**
end-stopped (or hypercomplex) cells **166**
feature detectors **168**
horizontal cells **161**
hyperphantasia **165**
koniocellular neurons **165**
lateral geniculate nucleus **161**
lateral inhibition **163**
magnocellular neurons **165**
parvocellular neurons **165**
primary visual cortex **165**
receptive field **163**
retinal disparity **170**
sensitive period **169**
simple cell **166**
strabismus **170**
V1 **165**

Thought Questions

1. After a receptor cell is stimulated, the bipolar cell receiving input from it demonstrates an immediate strong response. A fraction of a second later, the bipolar's response decreases, even though the stimulation from the receptor cell remains constant. How can you account for that decrease? (Hint: What does the horizontal cell do?)
2. A rabbit's eyes are on the sides of its head instead of in front. Would you expect rabbits to have many cells with binocular receptive fields—that is, cells that respond to both eyes? Why or why not?

Stop & Check Answers

12. It starts with the ganglion cells in the retina. Most of its axons go to the lateral geniculate nucleus of the thalamus, and others go to the superior colliculus and hypothalamus.
13. The receptor excites both the bipolar cells and the horizontal cell. The horizontal cell inhibits the same bipolar cell that was excited plus bipolar cells in the surround.
14. It produces more excitation than inhibition for the nearest bipolar cell. For surrounding bipolar cells, it produces only inhibition. The reason is that the receptor excites a horizontal cell, which inhibits all bipolar cells in the area.
15. In the parts of your retina that look at the long white arms, each neuron is inhibited by white input on two of its sides (either above and below or left and right). In the crossroads, each neuron is inhibited by input on all four sides. Therefore, the response in the crossroads is decreased compared to that in the arms.
16. They become larger because each cell's receptive field is made by inputs converging at an earlier level.
17. Neurons of the parvocellular system have small receptive fields, are located mostly in and near the fovea, and are specialized for details and color vision. Neurons of the magnocellular system have large receptive fields, occur throughout the retina, and are specialized for perceiving large patterns and movement.
18. Imagery activates area V1, just as vision does. However, the response is weaker and variable among individuals. Also, vision starts in V1 and spreads outward, whereas visual imagery starts in language and memory areas of the brain and gradually activates V1.
19. Area V1 is necessary for conscious vision, although certain types of visually guided behaviors can occur without conscious vision.

20. Identify a stimulus that stimulates the cell. Then present the stimulus in several locations. If the cell responds strongly in only one location, it is a simple cell. If it responds in several locations, it is a complex cell.

21. It is a neuron that detects the presence of a particular aspect of an object, such as a shape or a direction of movement.

22. When you look at something like the Mooney faces, it is possible to perceive it in more than one way.

23. If one eye is closed during early development, the cortex becomes unresponsive to it. If both eyes are closed, cortical cells remain somewhat responsive to them for several weeks and then gradually become sluggish and unselective in their responses.

24. Stereoscopic depth perception requires cells that compare the input from the two eyes. For children who have strabismus, no cell in the visual cortex gets matched inputs from the two eyes. Therefore, each cell becomes responsive to just one eye or the other.

25. Astigmatism results when the eyeball is not quite spherical. As a result, the person sees one direction of lines more clearly than the other.

26. The child sees well enough to identify whether two objects are the same or different, but at first the child doesn't understand what the visual information means. Understanding of vision improves with practice.

Module 5.2 | End-of-Module Quiz

1. What do horizontal cells in the retina do?

- **a.** They inhibit ganglion cells.
- **b.** They excite ganglion cells.
- **c.** They inhibit neighboring bipolar cells.
- **d.** They stimulate neighboring bipolar cells.

2. In humans, what crosses to the contralateral hemisphere at the optic chiasm?

- **a.** Half of each optic nerve, the part representing the nasal half of the retina
- **b.** Half of each optic nerve, the part representing the temporal half of the retina
- **c.** Nothing
- **d.** All of each optic nerve

3. What is the function of lateral inhibition in the retina?

- **a.** To sharpen borders
- **b.** To enhance colors
- **c.** To recognize objects
- **d.** To increase attention

4. Suppose light strikes the retina in a circle, surrounded by dark. Which bipolar cells will exhibit the greatest response, and which the least?

- **a.** Bipolar cells connected to receptors in the center of the circle respond the most. Those connected to receptors farthest from the circle respond the least.
- **b.** Bipolar cells connected to the receptors just outside the circumference of the circle respond most. Those connected to receptors just inside the circumference respond least.
- **c.** Bipolar cells connected to the receptors just inside the circumference of the circle respond most. Those connected to receptors just outside the circumference respond least.
- **d.** All bipolar cells within the circle will respond equally, and those outside will not respond at all.

5. Parvocellular cells are specialized to respond to what?

- **a.** Diffuse patterns
- **b.** Movement
- **c.** Vision in the periphery
- **d.** Color and detail

6. Magnocellular cells are specialized to respond to what?

- **a.** Color
- **b.** Movement
- **c.** Vision in the fovea
- **d.** Detail

7. Which of these is true of visual imagery?

- **a.** It is equally intense for nearly all people.
- **b.** It occurs without any change in brain activity.
- **c.** It occurs rapidly in V1 and then spreads to other brain areas.
- **d.** It starts in language or memory areas and spreads to V1.

8. Which of the following is responsible for many if not all cases of blindsight?

- **a.** Sprouting of auditory neurons into area V1
- **b.** Spontaneous neural activity in area V1
- **c.** Connections from V1 to other cortical areas
- **d.** Connections to cortical areas outside V1

9. How do complex cells in the visual cortex differ from simple cells?

- **a.** Complex cells make the same response after a stimulus moves.
- **b.** Complex cells respond to overall patterns, such as faces.
- **c.** Complex cells respond only to color, not shape.
- **d.** Complex cells respond only after receiving input from the prefrontal cortex.

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10. After you stare at a waterfall or other steadily moving display, you see stationary objects as moving in the opposite direction. That observation is evidence in favor of which of the following?

- **a.** Feature detectors
- **b.** Astigmatism
- **c.** Hyperphantasia
- **d.** Lateral inhibition

11. If a kitten has one eye shut for its first few weeks of life, its visual cortex becomes insensitive to that eye. Why?

- **a.** The receptors die.
- **b.** Any axon that is not used for that long becomes unable to respond.
- **c.** Activity from the active eye inhibits synapses from the inactive eye.
- **d.** The muscles controlling that eye become inactive.

12. If someone has dense cataracts on both eyes, and the cataracts are removed years later, what happens?

- **a.** The person remains permanently blind.
- **b.** The person gradually recovers all aspects of vision.
- **c.** The person has continuing limitations in depth and motion perception.
- **d.** The person has continuing limitations on color perception.

Answers: 1c, 2a, 3a, 4c, 5d, 6b, 7d, 8d, 9a, 10a, 11c, 12c.

Module 5.3

Specialized Visual Processes

Learning Objectives

After studying this module, you should be able to:

9. Distinguish between the ventral and dorsal streams of the visual system.

10. Describe the brain mechanisms for perceiving shapes, faces, and movement.

If you were working on an important business or government project, you might receive information on a need-to-know basis. If your job is to carry a particular package, you would need to know how heavy it is and whether it is fragile. Someone else who is keeping track of the finances would need to know how much the object costs and whether it needs insurance. A third person might open the package to check the color.

Similarly, different parts of the brain's visual system get information on a need-to-know basis. Cells that help your hand muscles reach out to an object need to know the size, location, shape, but they don't need to know about color. Cells that help you recognize people's faces need to be sensitive to details of shape, but they can pay less attention to location.

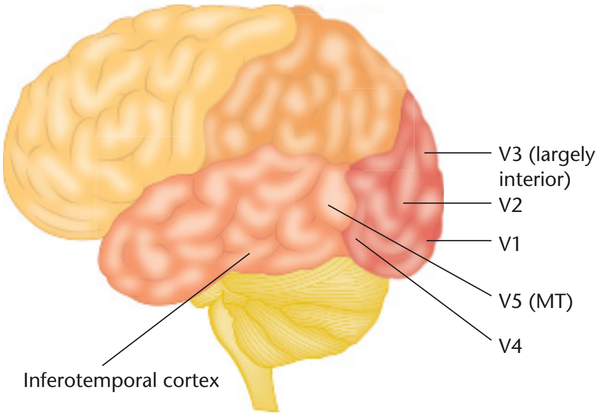
We tend to assume that anyone who sees an object sees everything about it—the shape, color, location, and movement. However, one part of your brain perceives its shape, another sees color, another detects location, and another perceives movement (Livingstone, 1988; Livingstone and Hubel, 1988; Zeki and Shipp, 1988). After localized brain damage, it is possible to perceive certain aspects of an object and not others. Centuries ago, people found it difficult to imagine how someone could see an object without seeing what color it is. Even today, you might find it surprising to learn about people who perceive an object without seeing where it is, or see it without seeing its movement.

The Ventral and Dorsal Streams

The primary visual cortex (V1) sends information to the **secondary visual cortex** (area **V2**), which processes the information further and transmits it to additional areas depicted in Figure 5.26. The receptive fields in V2 are more elongated than those of V1 (Liu et al., 2016), with many cells that respond to corners, textures, or complex shapes (Freeman et al., 2013). In areas V2 and V3, some cells are highly responsive to color, and other cells are highly responsive to the disparity between what the left and right eyes see—critical information for stereoscopic depth perception (Nasr et al., 2016). Area V4 has clusters of cells responsive to specific colors, including green, orange, and purple (Liu et al., 2020). When you imagine a colored object, V4 is the area that responds most strongly (Bannert and Bartels, 2018).

Figure 5.26 Some Major Visual Areas in Human Cortex

Information passes from V1 to V2 and from there to other areas. Connections are bidirectional. Each area also receives some information directly from the thalamus.



Researchers distinguish between the ventral stream and the dorsal stream. The **ventral stream** through the temporal cortex is the "what" pathway, because of its importance for identifying and recognizing objects. The **dorsal stream** through the parietal cortex is the "where" or "how" pathway, because of its importance for visually guided movements.

The distinction is based partly on animal studies, partly on MRI and fMRI studies (Milner, 2012), and partly on observations of patients with brain damage. A woman known as DF was exposed to carbon monoxide, causing damage mainly to the ventral stream—that is, the temporal cortex and its connections with the primary visual cortex (Bridge et al., 2013). She could not name the objects she saw, could not recognize faces, and could not even distinguish a square from a rectangle. When she was shown a slot in the wall, she could not say whether it was horizontal or vertical. Nevertheless, when she was asked to put an envelope through the slot, she aimed it correctly at once. When asked to guess the size of an object she sees, she performed at chance levels. However, when asked to pick up the object, she reached out correctly, adjusting her thumb and finger before touching the object (Whitwell et al., 2014). One man with temporal lobe damage could not describe the location of objects in his room, but when he walked, he accurately avoided obstacles in his way (Karnath et al., 2009). Another patient had such trouble recognizing objects by sight that she attached distinctive colored tapes to the important objects she needed to find in her house. However, she had no trouble reaching out to pick up any of the objects, once she had found it (Plant et al., 2015). In short, people with temporal lobe damage use vision to guide their actions, but they have trouble identifying what the objects are.

People with damage to the dorsal stream (parietal cortex) have the opposite problem: They can read, recognize faces, and describe objects in detail, but they cannot accurately reach out to grasp an object. While walking, they can describe what they see, but they bump into objects, oblivious to their location. Although they can describe from memory what their furniture looks like, they cannot remember where it is in the house (Kosslyn et al., 2001). They even seem uncertain where certain of their body parts are (Schenk, 2006). One patient had dorsal stream damage only in his left hemisphere. He demonstrated low accuracy at aiming his right arm or leg toward an object on the right side of his body. However, his accuracy was normal when aiming his left arm or leg toward either side, or when aiming his right arm toward the left side (Cavina-Pratesi et al., 2013).

Although the distinction between ventral and dorsal streams is useful, we should not overstate it. For people with intact visual cortices the two systems combine and share information in many ways (Donato et al., 2020).

Stop & Check

27. Suppose someone can describe an object in detail but stumbles and fumbles when trying to walk toward it and pick it up. Which is probably damaged, the dorsal stream or the ventral stream?

See page 183 for the answer.

Shape Perception

In Module 5.2, we encountered simple and complex cells of the primary visual cortex (V1). As visual information goes from the simple cells to the complex cells and then to other brain areas, the receptive fields become larger and more specialized. That is especially true for the inferior temporal cortex.

The Inferior Temporal Cortex

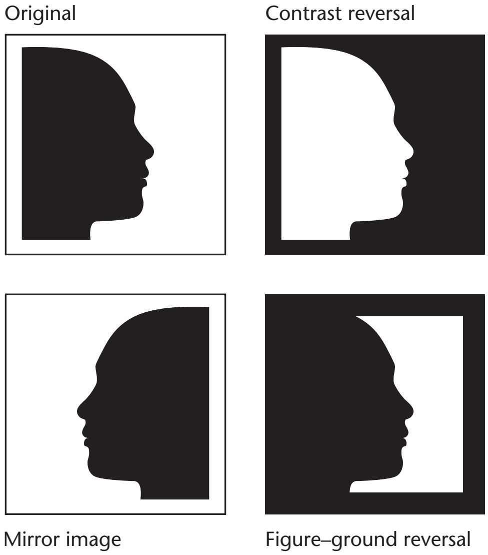
Cells in the **inferior temporal cortex** (Figure 5.26) learn to recognize familiar objects. A cell that learns to respond to the sight of an object initially responds mainly when it perceives it from the same angle, but after enough experience it responds from other viewpoints and distances (Murty and Arun, 2015). The inferior temporal cortex exchanges information with the prefrontal cortex with connections that are especially important for identifying difficult or ambiguous patterns (Kar and DiCarlo, 2021). One way to describe it is that the prefrontal cortex forms hypotheses about the object and feeds them back to the temporal cortex for confirmation or disconfirmation.

The inferior temporal cortex responds to more than just the patterns of light and dark that stimulate area V1. As depicted in Figure 5.27, cells in a monkey's inferior temporal cortex that responded strongly to the original profile responded about equally to its mirror image or contrast reversal, but not to a figure-ground reversal (Baylis and Driver, 2001). In terms of the pattern of light and dark, the figure-ground reversal is much like the original, but most people (and evidently monkeys also) see it as a white object on a black background, not as a face.

As we might expect, damage to the ventral pathway of the cortex leads to specialized deficits. **Visual agnosia** (meaning "visual lack of knowledge") is an inability to recognize objects despite otherwise satisfactory vision. One patient, when shown a key, said, "I don't know what

Figure 5.27 Transformations of a drawing

In the inferior temporal cortex, cells that respond strongly to the original respond about the same to the contrast reversal and mirror image but not to the figure–ground reversal. Note that the figure–ground reversal resembles the original in terms of the pattern of light and darkness, but it is not perceived as the same object.



(**Source:** Based on Baylis and Driver, 2001) that is. Perhaps a file or a tool of some sort." When shown a stethoscope, he said that it was "a long cord with a round thing at the end." When he could not identify a smoker's pipe, the examiner told him what it was. He then replied, "Yes, I can see it now," and pointed out the stem and bowl of the pipe. Then the examiner asked, "Suppose I told you that the last object was not really a pipe?" The patient replied, "I would take your word for it. Perhaps it's not really a pipe" (Rubens and Benson, 1971).

Within the inferior temporal cortex, several areas detect particular shapes, and brain damage can yield remarkable results. One man with brain damage could recognize almost anything he saw except the numbers 2 through 9, which always appeared to him as a tangle of black lines (Schubert et al., 2020). Part of the parahippocampal cortex (next to the hippocampus) responds mostly to the sight of places. Part of the **fusiform gyrus**, especially in the right hemisphere (Figure 5.28), responds mainly to faces. A neighboring area responds mostly to bodies (Downing et al., 2005; Kanwisher, 2010). The brain is remarkably adept at detecting the kinds of motion produced by people and animals. If you attach glow-in-the-dark dots to someone's elbows, knees, hips, shoulders, and a few other places, then when that person moves in an otherwise dark room, you perceive a moving person, even though you are watching only a few spots of light. You can view a wonderful demonstration by doing an Internet search for BioMotion Lab and then clicking on Demos.

Recognizing Faces

Face recognition is an important skill for humans. Civilization depends on knowing whether to trust or distrust someone, even someone you haven't seen in months or years. Someday when you attend a high school or college reunion, you are likely to recognize most of the people you knew well, even those who gained weight, became bald, or dyed their hair (Bruck et al., 1991).

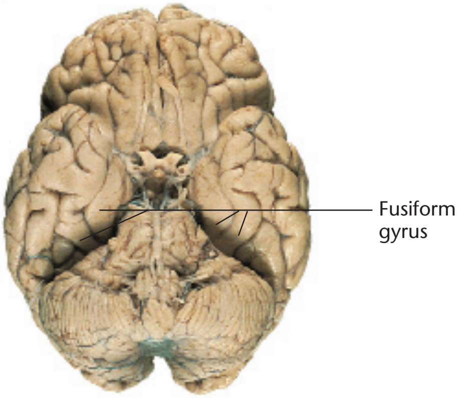
Human newborns come into the world predisposed to pay more attention to faces than other stationary displays (Figure 5.29). However, the infant's concept of "face" is not like an adult's. Experimenters recorded infants' times of gazing at one face or the other, as depicted in Figure 5.30. Newborns showed a strong preference for a right-side-up face over an upside-down face, regardless of whether the face was realistic (left pair) or distorted (central pair). When confronted with two right-side-up faces (right pair), they expressed no significant preference between a realistic one and a distorted one (Cassia et al., 2004).

The fusiform gyrus (Figure 5.28) responds strongly to a face viewed from any angle, as well as the memory of a face, a line drawing, or anything else that looks like a face (Caldara and Seghier, 2009; Kanwisher and Yovel, 2006; Khuvis et al., 2021). People are predisposed to see faces wherever possible. Just draw two dots and an upward curved line below them, and people call it a "smiley face." Children's accuracy at identifying faces improves as connections strengthen between the right hemisphere fusiform gyrus and part of the occipital cortex known as the occipital face area (Song et al., 2015). Cortical cells that respond strongly to faces also respond somewhat to face-like objects (Decramer et al., 2021). Refer to Figure 5.31.

In several cases, physicians electrically stimulated the fusiform gyrus during exploratory surgery. Depending on the intensity and duration of stimulation, the result was either a difficulty in perceiving faces (S. C. Chong et al., 2013) or a vivid distortion of faces. One patient exclaimed, "You just turned into somebody else. Your face metamorphosed" (Parvizi et al., 2012, p. 14,918). Monkeys also have trouble recognizing faces during electrical stimulation of an area corresponding to the fusiform gyrus (Moeller et al., 2017).

Figure 5.28 The fusiform gyrus

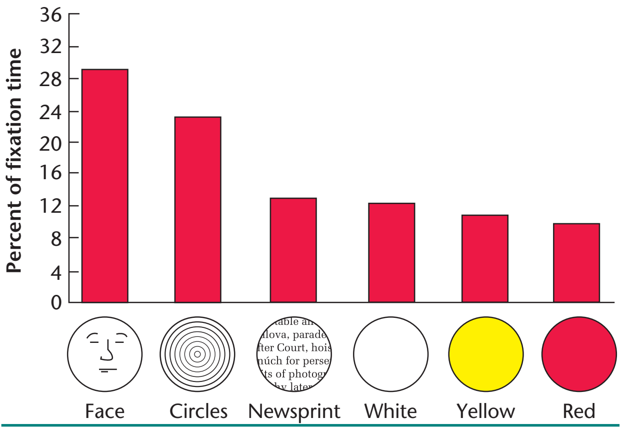
Many cells here are especially active during recognition of faces.



(**Source:** Courtesy of Dr. Dana Copeland)

Figure 5.29 Amount of time infants spend looking at patterns

Even in the first 2 days after birth, infants look more at faces than at most other stimuli.



(**Source:** Based on Fantz, 1963)

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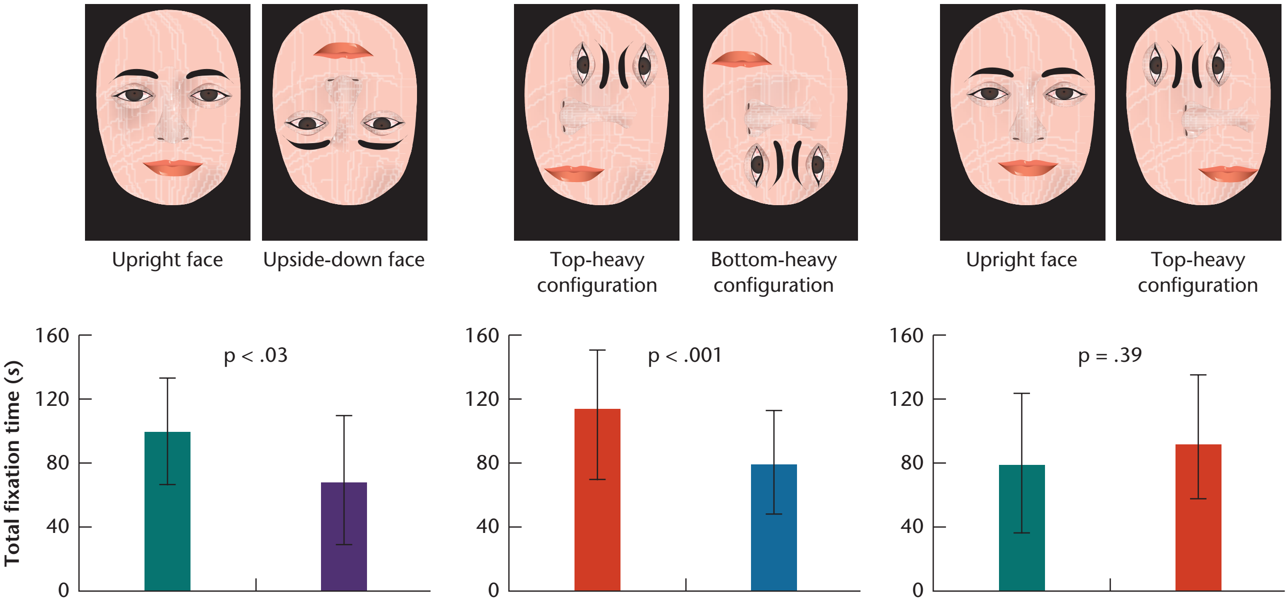
Figure 5.30 How infants divided their attention between faces

A right-side-up face drew more attention than an upside-down one, regardless of whether the faces were realistic (left pair) or distorted (central pair). Infants divided their attention about equally between two right-side-up faces (right pair), even though one was realistic and the other was distorted.

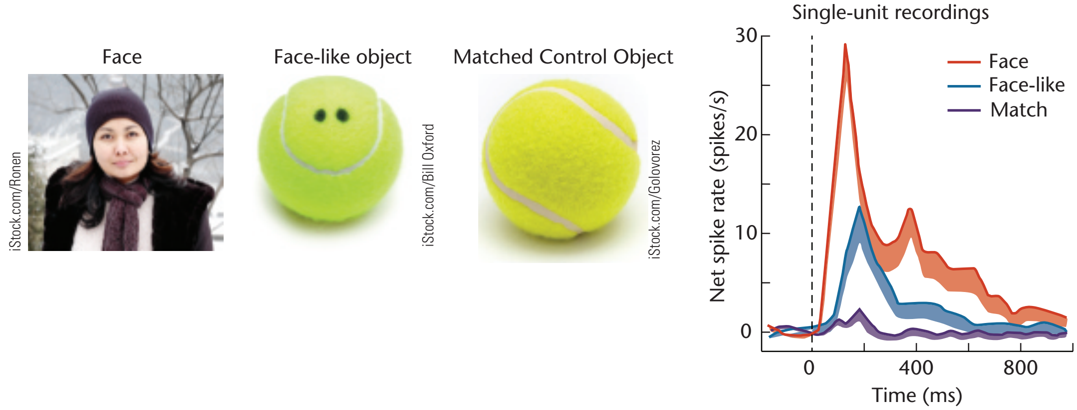


(**Source:** From "Can a nonspecific bias toward top-heavy patterns explain newborns' face preference?" by V. M. Cassia, C. Turati, & F. Simion, 2004. *Psychological Science, 15*, 379–383.)

People vary considerably in their ability to recognize faces, and not because of a lack of interest. People with the worst recognition are said to have **prosopagnosia** (PROSS-oh-pag-NOH-see-ah), meaning impaired ability to recognize faces. That problem can result from damage to the right fusiform gyrus, failure of that gyrus to develop fully, or fewer than normal connections between it and the occipital cortex (Grueter et al., 2007; Lohse et al., 2016; C. Thomas et al., 2009; Zhang et al., 2015; Zhu et al., 2011). At the opposite extreme, "super-recognizers," who have richer than average connections between fusiform gyrus and occipital cortex, easily recognize people they saw only once or twice long ago, and they accurately recognize celebrities from photos taken long before they became famous (Tardif et al., 2019).

Figure 5.31 How cells sensitive to faces react to other objects

This cell exhibited a strong response to faces and an intermediate response to objects that could be perceived as face-like. From Decreamer et al. (2021).



(**Source:** From Decreamer, et al. (2021).)

Oliver Sacks, famous for writing about other people's neurological problems, suffered from prosopagnosia himself. In his words, "I have had difficulty recognizing faces for as long as I can remember. I did not think too much about this as a child, but by the time I was a teenager, in a new school, it was often a cause of embarrassment. . . . My problem with recognizing faces extends not only to my nearest and dearest but also to myself. Thus, on several occasions I have apologized for almost bumping into a large bearded man, only to realize that the large bearded man was myself in a mirror. The opposite situation once occurred at a restaurant. Sitting at a sidewalk table, I turned toward the restaurant window and began grooming my beard, as I often do. I then realized that what I had taken to be my reflection was not grooming himself but looking at me oddly" (Sacks, 2000, p. 37)

People with prosopagnosia recognize people's voices, so the problem is not memory (Farah et al., 1998). They can read, so visual acuity is not the problem. They can describe each element of a face, such as brown eyes, big ears, or a small nose. They can also identify facial expressions of emotion (Towler et al., 2017), and they are close to normal at looking at photos of faces, side by side, and saying whether they are the same or different (White et al., 2017). The problem seems to be one of seeing a face as a whole and recognizing it. You might demonstrate a bit of this problem if you viewed photos upside-down. You could describe the size of the nose, ears, and so forth, but you might not recognize the person, at least not quickly.

One patient was shown 34 photographs of famous people and had a choice of two identifications for each. By chance alone, he should have identified 17 correctly; in fact, he got 18. He remarked that he seldom enjoyed watching movies or television programs because he had trouble keeping track of the characters. Curiously, his favorite movie was *Batman*, in which the main characters wore masks much of the time (Laeng and Caviness, 2001).

Did we really evolve a brain module devoted to faces? The other hypothesis is that we evolved mechanisms for recognizing complex patterns, of which faces happen to be the best and most common example (Arcaro and Livingstone, 2021). Children with an intense interest in Pokemon cards exhibit strong response in the fusiform gyrus when they look at Pokemon characters (James and James, 2013). Chess experts express a response there when they look at a chessboard (Bilalic et al., 2011). One study found that children who devoted at least an hour a day to some special interest, such as watching soccer or looking at pictures of space travel, demonstrated fusiform gyrus responses to images related to that interest. The response to other items was even greater for children with autism spectrum disorder, who pay less than usual attention to faces (Foss-Feig et al., 2016).

Evidently the fusiform gyrus participates in many types of detailed visual recognition. Still, even in people with extreme levels of expertise at recognizing something else, many cells in the fusiform gyrus respond more vigorously to faces (Kanwisher and Yovel, 2006). Additional evidence for a predisposition is that people who were blind from birth exhibit elevated activity in the fusiform gyrus when they feel models of faces (Ratan Murty et al., 2020). Researchers used a modified MRI procedure to record brain activity from 2–9-year-old infants. They found that the fusiform gyrus responded mainly to faces, just as it does in adults. Evidently this area is specialized for faces from the start (Kosakowski et al., 2022).

Stop & Check

28. How do responses in the inferior temporal cortex differ from those in V1?
29. The ability to recognize faces correlates with the strength of connections between which brain areas?

See page 183 for the answer.

Motion Perception

Any moving object merits your attention. It might be a possible mate, something you could hunt and eat, or something that wants to eat you. You need to identify where it is going, and how fast. The brain is set up to make those calculations quickly.

The Middle Temporal Cortex

Two areas especially important for motion perception are area **MT** (for middle temporal cortex), also known as area **V5** (Figure 5.27), and an adjacent region, area **MST** (medial superior temporal cortex). These areas receive input mostly from the magnocellular path (Nassi and Callaway, 2006), which detects overall patterns and movement. Given that the magnocellular path is color insensitive, MT is also color insensitive.

Most cells in area MT respond selectively when something moves at a particular speed in a particular direction (Perrone and Thiele, 2001). MT cells detect acceleration or deceleration as well as absolute speed (Schlack et al., 2007), and they respond to motion in all three dimensions (Rokers et al., 2009). Area MT also responds to photographs that imply movement, such as a photo of people running (Kourtzi and Kanwisher, 2000). People who have electrical stimulation of area MT (while undergoing exploratory studies to find the cause of their epilepsy) report seeing vibrations or other movements during the stimulation (Rauschecker et al., 2011). They also become temporarily impaired at seeing something that really is moving (Becker et al., 2013). In short, MT activity is apparently central to the experience of seeing motion. Cells in the dorsal part of area MST respond to more complex stimuli, such as the expansion, contraction, or rotation of a scene, as illustrated in Figure 5.32. That kind of experience occurs when you move forward or backward or tilt your head.

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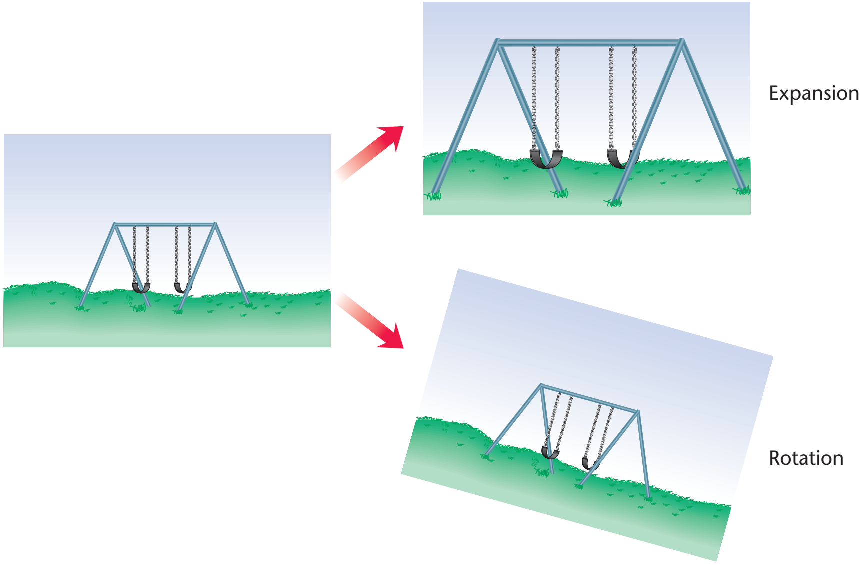
Figure 5.32 Stimuli that excite the dorsal part of area MST

Cells here respond if a whole scene expands, contracts, or rotates. That is, they respond if the observer moves forward or backward or tilts his or her head.



When you move your head or eyes from left to right, everything in your visual field moves across your retina as if the world itself had moved right to left. (Go ahead and try it.) Yet the world seems stationary, because nothing moved relative to anything else. Neurons in areas MT and the ventral part of MST respond briskly if something moves relative to the background, but they exhibit little response if the object and the background both move in the same direction and speed (Takemura et al., 2012). In short, MT and MST neurons enable you to distinguish between the result of eye movements and the result of object movements.

Motion Blindness

Given that areas MT and MST respond strongly to moving objects, and only to moving objects, what would happen after damage to these areas? The result is **motion blindness**, being able to see objects but unable to see whether they are moving or, if so, which direction and how fast (Marcar et al., 1997). People with motion blindness are better at reaching for a moving object than at describing its motion (Schenk et al., 2000), but in all aspects of dealing with visual motion, they are far behind other people.

Motion blindness in the absence of other dysfunction is a rare condition. The best described case, "LM," reported that she felt uncomfortable when people walked around because they "were suddenly here or there but I have not seen them moving." People would seem to appear or disappear suddenly, even when she was trying to keep track of them. Someone who was walking would appear to her as "restless," but she would not know which direction the person was going. She would find it so unsettling that she would stop her own walking until the other person was gone. She could not cross a street without help, because she could not tell which cars were moving, or how fast. Pouring coffee became difficult. The flowing liquid appeared to be frozen and unmoving, so she did not stop pouring until the cup overfilled (Zihl et al., 1983; Zihl and Heywood, 2015).

People with full color vision can imagine what it would be like to be color deficient, but it is difficult to imagine having motion blindness. If something is moving, and you detect it, how could you fail to see that it is moving? Because this experience seems so odd, neurologists for many years resisted the idea of motion blindness. Several patients were reported who apparently became motion blind after brain damage, but most scientists ignored or disbelieved the reports. After the discovery of area MT from monkey research, researchers saw a mechanism whereby motion blindness could occur, and they came to accept the reports of motion blindness.

Try It Yourself

You wonder what it would be like to be motion blind. Try this demonstration: Look at yourself in a mirror and focus on your left eye. Then shift your focus to your right eye. (*Please do this now.*) Did you see your eyes move? No, you did not. (*Oh, please try the demonstration!*)

Why didn't you see your eyes move? Your first impulse is to say that the movement was too small or too fast. Wrong. Try looking at someone else's eyes who focuses first on one of your eyes and then the other. You *do* see the other person's eyes move, even though they moved the same distance and the same speed as your own. An eye movement is neither too small nor too fast for you to see.

You do not see your own eyes move because area MT and parts of the parietal cortex decrease their activity during voluntary eye movements, known as **saccades** (Bremmer, Kubischik, Hoffmann, & Krekelberg, 2009). (They do not decrease their activity while your eyes follow a moving object.) The brain areas that monitor saccades tell area MT and the parietal cortex, "We're about to move the eye muscles, so take a rest for the next split second." Neural activity and blood flow in MT and part of the parietal cortex begin to decrease 75 milliseconds (ms) before the eye movement and they remain suppressed during the movement (Burr et al., 1994; Paus et al., 1995; Vallines and Greenlee, 2006). In short, during a voluntary eye movement, you become motion blind for a split second. Perhaps now you understand a little better what people with motion blindness experience all the time.

The opposite of motion blindness also occurs: Some people are blind *except* for the ability to detect movement. How could someone see movement without seeing the object that is moving? Area MT gets input directly from the lateral geniculate nucleus of the thalamus. Even after extensive damage to area V1 (enough to produce blindness), area MT still has enough input to permit motion detection (Sincich et al., 2004). Again, we try to imagine this person's experience. What would it be like to see motion without seeing the objects that are moving? (This is blindsight, and their answers don't help. When they say which direction something is moving, they insist they are just guessing.) The general point is that different areas of your brain process different kinds of visual information, and it is possible to develop specialized kinds of disability.

Stop & Check

30. When you move your eyes, why does it not seem as if the world is moving?
31. Under what circumstance does someone with an intact brain become motion blind, and what accounts for the motion blindness?

See page 183 for the answer.

Module 5.3 | In Closing

Aspects of Vision

Anatomists have identified nearly a hundred brain areas that contribute to vision. Why do we have so many visual areas? We can only infer that the brain, like a human society, benefits from specialization. Life works better if some people become experts at repairing cars, some at baking cakes, some at delivering babies, and some at moving pianos. Similarly, your visual system works better because visual areas specialize in a particular task without trying to do everything.

A related question: How do you put it all together? When you watch a bird fly by, you perceive its shape, color, location, and movement as a single object. How do you do that? This is the binding problem, as discussed in Chapter 3. Answering that question remains a major challenge.

Summary

1. Researchers distinguish between the ventral visual stream, responsible for perceiving objects and the dorsal stream, responsible for visual guidance of movements. **176**
2. Damage to the ventral stream can lead to visual agnosia, an inability to recognize or identify objects. **176**
3. The inferior temporal cortex detects objects and recognizes them despite changes in position, size, and angle. **177**
4. The fusiform gyrus and its connections to the occipital cortex are specialized for recognizing faces. People with impairments in this circuit experience prosopagnosia, a difficulty in recognizing faces despite normal vision in other regards. **178**
5. The middle temporal cortex (including areas MT and MST) is specialized for detecting the direction and speed of a moving object. People with damage in this area experience motion blindness, an impairment in their ability to perceive movement. **180**
6. Even people with an intact brain experience a brief period of motion blindness beginning about 75 ms before a voluntary eye movement and continuing during the eye movement. **181**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with

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definitions in the book's Subject Index/Glossary at the end of this book.

dorsal stream	**176**
fusiform gyrus	**178**
inferior temporal cortex	**177**
motion blindness	**181**
MST	**180**
MT (or area V5)	**180**
prosopagnosia	**179**
saccade	**182**
secondary visual cortex	**176**
ventral stream	**176**
visual agnosia	**177**

Stop & Check Answers

Thought Questions

1. The visual system has specialized areas for perceiving faces, bodies, and places but not other kinds of objects. Why might we have evolved specialized areas for these functions but not others?
2. Why is it advantageous to become motion blind during voluntary eye movements? That is, why might we have evolved this mechanism?

27. The inability to guide movement based on vision implies damage to the dorsal stream.
28. Cells in V1 respond to patterns of light and dark. Cells in the inferior temporal cortex respond to a particular shape or object, even if the areas of light and dark are reversed.
29. Ability to recognize faces correlates with the strength of connections between the fusiform gyrus and the occipital face area.
30. Neurons in areas MT and MST respond strongly when an object moves relative to the background, but not when the object and background move together.
31. People become motion blind shortly before and during a saccade (voluntary eye movement), because of suppressed activity in area MT.

Module 5.3 | End-of-Module Quiz

1. The dorsal stream of the visual system is specialized for which of these?
   - **a.** Perception of color
   - **b.** Coordinating vision with movement
   - **c.** Peripheral vision and vision under poor lighting
   - **d.** Detailed identification of objects

2. What happens to receptive fields as we progress from V1 to V2, V3, and beyond?
   - **a.** They become more sensitive to the periphery of vision.
   - **b.** They become less sensitive to color.
   - **c.** They become larger and more complicated.
   - **d.** They become smaller and simpler.

3. What is distinctive about visual perception in the inferior temporal cortex?
   - **a.** Cells respond only during times of both sight and sound.
   - **b.** Cells respond in proportion to the brightness of light.
   - **c.** Cells respond only to objects that are moving at a particular speed.
   - **d.** Cells respond to an object regardless of the angle of view.

4. The fusiform gyrus is specialized for which of the following?
   - **a.** Recognizing faces and other highly familiar objects
   - **b.** Maintaining color recognition despite changes in room lighting
   - **c.** Identifying the direction and speed of a visual object
   - **d.** Coordinating vision with hearing and other senses

5. If someone has trouble recognizing faces, what pathway in the nervous system is probably deficient?
   - **a.** Connections between the primary visual cortex and area MT
   - **b.** Connections between the fusiform gyrus and part of the occipital cortex
   - **c.** Connections between the temporal cortex and the parietal cortex
   - **d.** Connections between the occipital cortex and the primary motor cortex

6. What happens after damage limited to area MT?
   - **a.** Motion blindness
   - **b.** Face blindness
   - **c.** Color blindness
   - **d.** Night blindness

7. Why is it difficult to watch your own eyes move when looking in the mirror?
   - **a.** The eye movements are too fast to see.
   - **b.** The eye movements are too small to see.
   - **c.** During a saccadic eye movement, the eyes do not move relative to the background of the rest of the face.
   - **d.** During saccadic eye movements, activity decreases in area MT.

Answers: 1b, 2c, 3d, 4a, 5b, 6a, 7d.

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Suggestions for Further Reading

Hoffman, D. (2019). *The case against reality*. (W. W. Norton)

How could you possibly resist a book with that title? Hoffman highlights the case that our senses provide us with an uncertain and incomplete knowledge of reality.

Masland, R. (2020). *We know it when we see it.* (Basic books)

This first-person account of the experiences of being a vision researcher gives thought-provoking insights as well as a clear description of current knowledge.

Purves, D., & Lotto, R. B. (2003). *Why we see what we do: An empirical theory of vision.* (Sinauer Associates)

This presents a discussion of how our perception of color, size, and other visual qualities depends on our previous experience with objects and not just on the light striking the retina.

Sacks, O. (2010). *Mind's eye.* (Alfred Knopf)

Here are case histories of people with brain damage who lost the ability to recognize faces, the ability to read, the ability to find their way around, and other visual abilities.

Chapter 6

The sensory world of bats—which find insects by echolocation—must be very different from that of humans.

(Md Imrul Kayes/Dreamstime.com)

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Hearing, the Mechanical Senses, and the Chemical Senses

Chapter Outline

Module 6.1

Hearing

Sound and the Ear
Pitch Perception
The Auditory Cortex
Sound Localization
Individual Differences
In Closing: Functions of Hearing

Module 6.2

The Mechanical Senses

Vestibular Sensation
Somatosensation
Pain
Itch
In Closing: The Mechanical Senses

Module 6.3

The Chemical Senses

Taste
Olfaction
Synesthesia
In Closing: Senses as Ways of Knowing the World

Learning Objectives

After studying this chapter, you should be able to:

1. Describe the receptors for hearing.
2. Explain the mechanisms of pitch perception and sound localization.
3. Describe the functions of the primary auditory cortex.
4. Discuss causes of hearing loss.
5. Describe the mechanisms of vestibular sensation and somatosensation.
6. Compare physical and emotional pain.
7. Describe methods of relieving pain.
8. Describe the mechanisms of taste and smell.
9. Discuss individual differences in taste and olfaction.
10. Define and describe synesthesia.

According to a Native American saying, “A pine needle fell. The eagle saw it. The deer heard it. The bear smelled it” (Herrero, 1985).

Each species responds to the most useful kinds of information. Some birds have receptors to detect magnetic fields, useful information for migratory flight (Mouritsen, 2018). The ears of the green tree frog detect mainly the frequencies prominent in the male’s mating call (Moss and Simmons, 1986). Mosquitoes evolved a special receptor that detects the odor of human sweat, which helps them find us and bite us (McBride et al., 2014). Bats locate insects by emitting sonar waves well above the range of adult human hearing (Griffin, Webster, and Michael, 1960), and then they locate insects from the echoes. Some moths jam the signals by emitting similar high-frequency calls of their own (Corcoran, Barber, and Conner, 2009).

Humans, too, have sensory specializations. As Donald Hoffman (2019) emphasized, our sense organs evolved to help us survive and reproduce. Whatever they tell us about reality is just a nice byproduct. Our vision and hearing register only limited ranges of electromagnetic radiation and air waves. Our sense of taste alerts us to the bitterness of poisons (Richter, 1950; Schiffman and Erickson, 1971) and it ignores substances such as cellulose that neither help nor harm us. Our olfactory systems ignore gases that we don't need to detect (e.g., nitrogen) but they respond strongly to the smell of rotting meat. This chapter is about how hearing, the mechanical senses, and the chemical senses give us useful information.

Module 6.1

Hearing

Learning Objectives

After studying this module, you should be able to:

1. Describe the receptors for hearing.
2. Explain the mechanisms of pitch perception and sound localization.
3. Describe the functions of the primary auditory cortex.
4. Discuss causes of hearing loss.

Evolution has been described as "thrifty." After it has solved one problem, it modifies that solution for other problems instead of starting from scratch. Imagine a gene for visual receptors in an early vertebrate. Make a duplicate of that gene, modify it slightly, and presto: The new gene makes receptors that respond to other wavelengths of light. In this chapter, there are more examples of that principle. Sensory systems have their specializations, but they also have much in common.

Sound and the Ear

We attend to hearing to extract useful information. If you hear footsteps in your home or a snapped twig in the forest, you know you are not alone. If you hear breathing, you know a person or animal is close. If you recognize the sound of a familiar voice, you know that all is well. Under optimum conditions, human hearing is sensitive to sounds that vibrate the eardrum by less than one-tenth the diameter of an atom, and some people can detect a difference between sounds as little as 1/30 the interval between two piano notes (Hudspeth, 2014).

Physics and Psychology of Sound

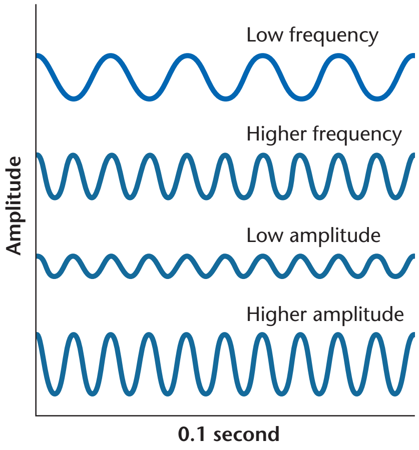
Sound waves are periodic compressions of air, water, or other media, varying in amplitude and frequency. The **amplitude** of a sound wave is its intensity. In general, sounds of greater amplitude seem louder, but a rapidly talking person seems louder than slow music of the same amplitude.

The **frequency** of a sound is the number of compressions per second, measured in hertz (Hz, cycles per second). **Pitch** is the related aspect of perception. Sounds higher in frequency are higher in pitch. Figure 6.1 illustrates the amplitude and frequency of sounds. The height of each wave represents the amplitude, and the number of waves per second represents the frequency.

Most adult humans hear sounds from about 15 to 20 Hz up to almost 20,000 Hz. Children hear higher

Figure 6.1 Four sound waves

The top line represents five sound waves in 0.1 second, or 50 Hz—a low-frequency sound that we experience as a low pitch. The other three lines represent 100 Hz. The vertical extent of each line represents its amplitude, which we experience as loudness.



frequencies, because the ability to perceive high frequencies decreases with age and exposure to loud noises. As a rule, larger animals like elephants hear best at lower frequencies, and small animals like mice hear higher frequencies, above what humans hear. You may be familiar with dog whistles that dogs can hear but humans can't.

In addition to amplitude and pitch, the third aspect of sound is **timbre** (TAM-ber), meaning tone quality or tone complexity. Different musical instruments playing the same note sound different, as do people singing the same note. An instrument playing a note at any frequency also produces notes at multiples of that frequency, the harmonics of the principal note. The harmonics differ among instruments.

People communicate emotion by alterations in pitch, loudness, and timbre. Conveying emotional information by tone of voice is known as *prosody.* For example, the way you say "that was interesting" could indicate approval (it really was interesting), sarcasm (it really was boring), or suspicion (you think someone was hinting something). "What are you doing?" could indicate curiosity, anger, or amusement.

Structures of the Ear

Rube Goldberg (1883–1970) drew cartoons of complicated, far-fetched inventions. A person's tread on the front doorstep might pull a string that raised a cat's tail, awakening the cat, which then chases a bird that had been resting on a balance, which swings up to strike a doorbell. The functioning of the ear is complex enough to resemble a Rube Goldberg device. (Desperate for some entertainment right now? You could do a YouTube search for Rube Goldberg device. But do come back to finish your reading.)

Anatomists distinguish the outer ear, the middle ear, and the inner ear (Figure 6.2). The outer ear includes the **pinna**, the familiar structure of flesh and cartilage attached to each side of the head. By altering the reflections of sound waves, the pinna helps us locate the source of a sound. We have to learn to use that information because all pinnas are shaped differently (Van Wanrooij and Van Opstal, 2005). Rabbits' large movable pinnae enable them to localize sound sources even more precisely.

Sound waves passing through the auditory canal (Figure 6.2) enter the middle ear, a structure that had to evolve when ancient fish evolved into land animals. Because animal tissues respond to water vibrations almost the same way that water itself does, fish have relatively simple hearing receptors that would not respond well to vibrations in the air (Christensen et al., 2015). The structures of the middle ear and inner ear evolved to amplify sound vibrations.

When sound waves reach the middle ear, they vibrate the **tympanic membrane**, or eardrum. The tympanic membrane connects to three tiny bones that transmit the vibrations to the **oval window**, a membrane of the inner ear. These bones, the smallest bones in the body, are sometimes known by their English names (hammer, anvil, and stirrup) and sometimes by their Latin names (malleus, incus, and stapes). As in a hydraulic pump, the vibrations of the tympanic membrane amplify into more forceful vibrations of the smaller stirrup, converting sound waves into waves of greater pressure on the oval window.

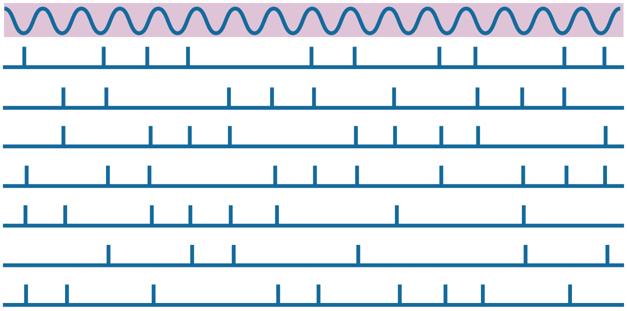
When the stirrup vibrates the oval window, it sets into motion the fluid in the **cochlea** (KOCK-lee-uh), the snail-shaped structure of the inner ear. Figure 6.2 illustrates a cross-section through the cochlea and its tunnels. The auditory receptors, known as **hair cells**, lie along the basilar membrane of the cochlea (Figure 6.2d). Vibrations in the fluid of the cochlea displace the hair cells, which stimulate the auditory nerve. Figure 6.3 depicts an electron micrograph of human hair cells.

Pitch Perception

To understand speech or enjoy music you have to detect the frequencies of sounds. Your auditory system uses two mechanisms.

According to the **frequency theory** in its original form, the basilar membrane vibrates in synchrony with sound waves, causing auditory nerve axons to produce action potentials at the same frequency. For example, a sound at 50 Hz would cause 50 action potentials per second in the auditory nerve. The downfall of this theory in its simplest form is that the refractory period limits the maximum firing rate of any neuron to about 1000 Hz, far short of the highest frequencies we hear.

Although any single receptor is limited in its firing frequency, a group of receptors can have a pattern like the one represented below. Each sound wave produces responses in the receptors that are phase-locked to the sound wave but not to one another. In this way the auditory nerve can produce volleys of impulses for sounds up to about 4,000 per second, even though no individual axon approaches that frequency (Rose et al., 1967). A soft tone stimulates fewer neurons for each peak of the sound wave, and louder tones stimulate progressively more of them.



James W. Kalat

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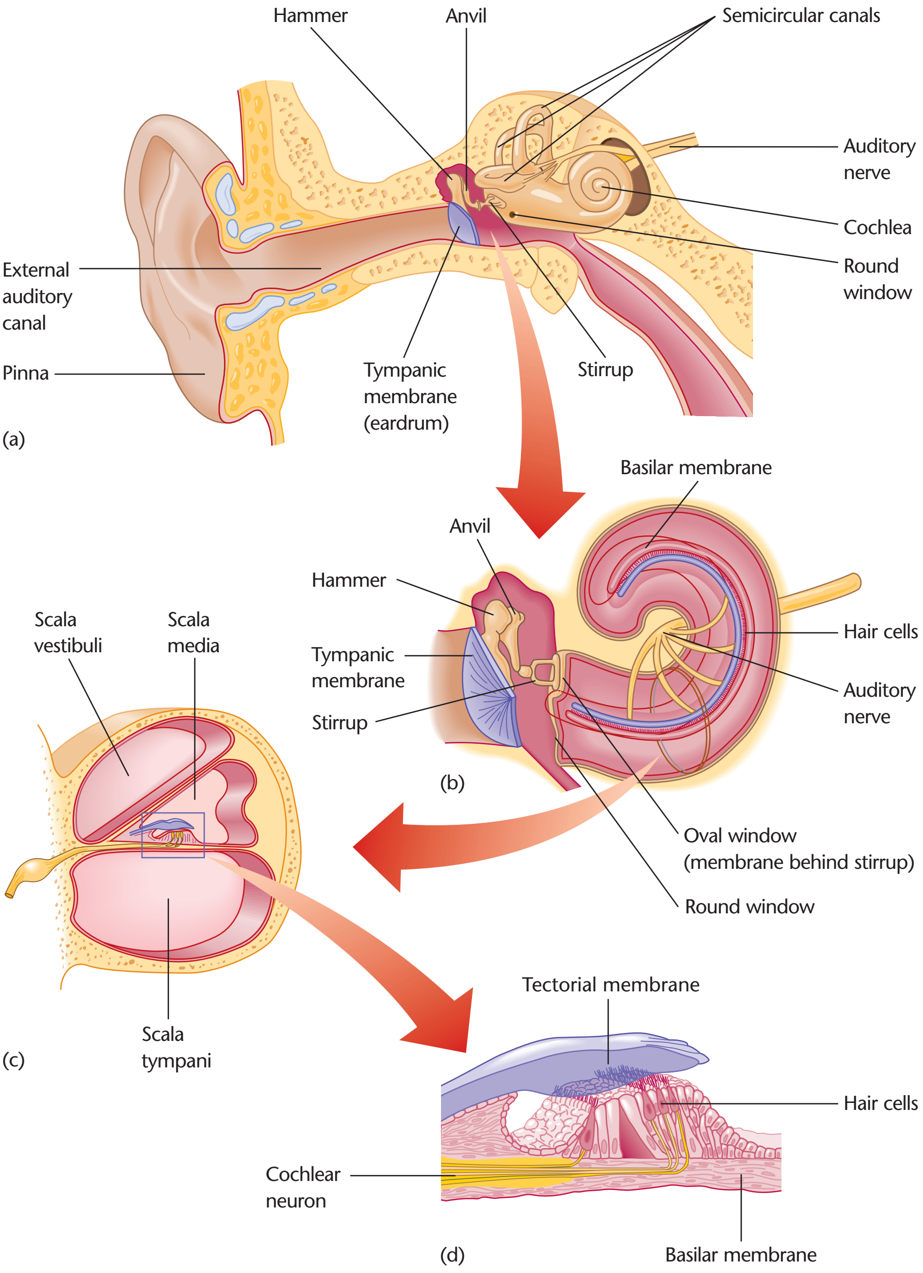
Figure 6.2 Structures of the ear

When sound waves strike the tympanic membrane in (a), they vibrate three tiny bones—the hammer, anvil, and stirrup—that convert the sound waves into stronger vibrations in the fluid-filled cochlea (b). Those vibrations displace the hair cells along the basilar membrane in the cochlea. (c) A cross-section through the cochlea. (d) A close-up of the hair cells.


Hammer
Anvil
Semicircular canals
Auditory nerve
Cochlea
Round window
External auditory canal
Pinna
Tympanic membrane (eardrum)
Stirrup
(a)
Basilar membrane
Anvil
Hammer
Hair cells
Tympanic membrane
Auditory nerve
Stirrup
(b)
Scala vestibuli
Scala media
Oval window (membrane behind stirrup)
Round window
Scala tympani
(c)
Tectorial membrane
Hair cells
Cochlear neuron
(d)
Basilar membrane

The second mechanism of pitch perception is the **place theory**. Originally, this theory suggested that the basilar membrane resembles the strings of a piano. If you sound a note with a tuning fork near a piano, you vibrate the piano string tuned to that note. However, the parts of the basilar membrane are bound together too tightly for any part to resonate like a piano string.

A modified version of place theory is this: The basilar membrane varies from stiff at its base, where the stirrup meets the cochlea, to floppy at the other end of the cochlea,

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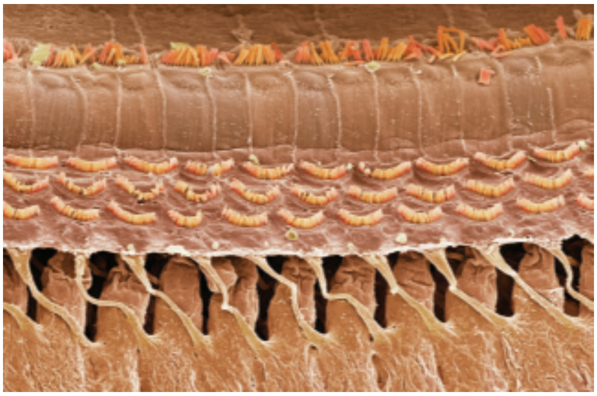
Figure 6.3 Hair cells from a human cochlea

This artificially colored electron micrograph depicts stereocilia (the crescent-shaped structures across the center of the photo) atop hair cells. As a sound wave moves the fluid across the stereocilia, it bends them, triggering responses by the hair cells.

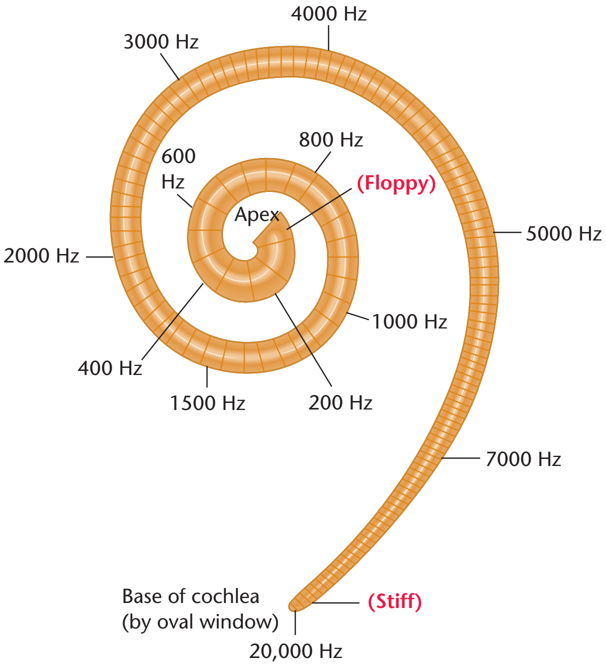


SPL/Science Source

the apex (Figure 6.4). A high-pitched sound sets up a traveling wave that peaks sharply at some point along the basilar membrane. The point at which it peaks identifies the frequency of the sound. Low frequency sounds vibrate hair cells near the apex, and high frequency sounds vibrate hair cells farther toward the base (Hudspeth, 2014; Warren, 1999).

Figure 6.4 Basilar membrane of the human cochlea

High-frequency sounds excite hair cells near the base. Low-frequency sounds excite cells near the apex.



Stop & Check

1. Which theory is based on the rate of firing by each neuron?
2. Which theory is based on which neurons fire?
3. Which theory explains how we hear the highest frequency sounds, above 4000 Hz?

See page 196 for the answer.

The Auditory Cortex

As information from the auditory system passes through subcortical areas, axons cross over in the midbrain to enable each hemisphere of the forebrain to get most of its input, but not all of it, from the opposite ear. The information ultimately reaches the **primary auditory cortex (area A1)** in the superior temporal cortex, as illustrated in Figure 6.5.

The organization of the auditory cortex parallels that of the visual cortex (Poremba et al., 2003). Like the visual system, the auditory system has a "what" pathway and a "where" or "how" pathway. The "what" pathway combines input from the auditory system and the visual system (important when you watch people's lips to help understand what they are saying), and it connects to systems for memory and decision-making. The "where" or "how" pathway localizes sound sources and guides actions toward or away from them (Jasmin et al., 2019).

An area in the temporal cortex called the *planum temporale* processes the experience you have of a sound source moving from one place to another. That area is strongly connected to area MT, which processes visual motion (Gurtubay-Antolin et al., 2021). The connection helps you combine visual and auditory information to locate something accurately. Just as patients with damage in area MT become motion blind, patients with damage in the planum temporale become motion deaf. They hear sounds, but they do not detect that a sound source is moving (Ducommun et al., 2004).

Just as area V1 is active during visual imagery, area A1 responds to imagined sounds. It becomes active when people view silent videos that suggest sound—such as someone playing a piano or a glass vase shattering on the ground (K. Meyer et al., 2010). In one study, people listened to familiar and unfamiliar songs. At various points, parts of each song were replaced by 3- to 5-second gaps. When people were listening to familiar songs, they reported that they heard "in their heads" the notes or words that belonged in the gaps, and area A1 exhibited activity similar to normal hearing. During similar gaps in the unfamiliar songs, they did not hear anything in their heads, and area A1 exhibited no response (Kraemer et al., 2005).

Also like the visual system, the auditory system's development depends on experience. Just as rearing an animal with its eyes closed impairs visual development, rearing one in constant noise impairs auditory development (Chang and Merzenich, 2003).

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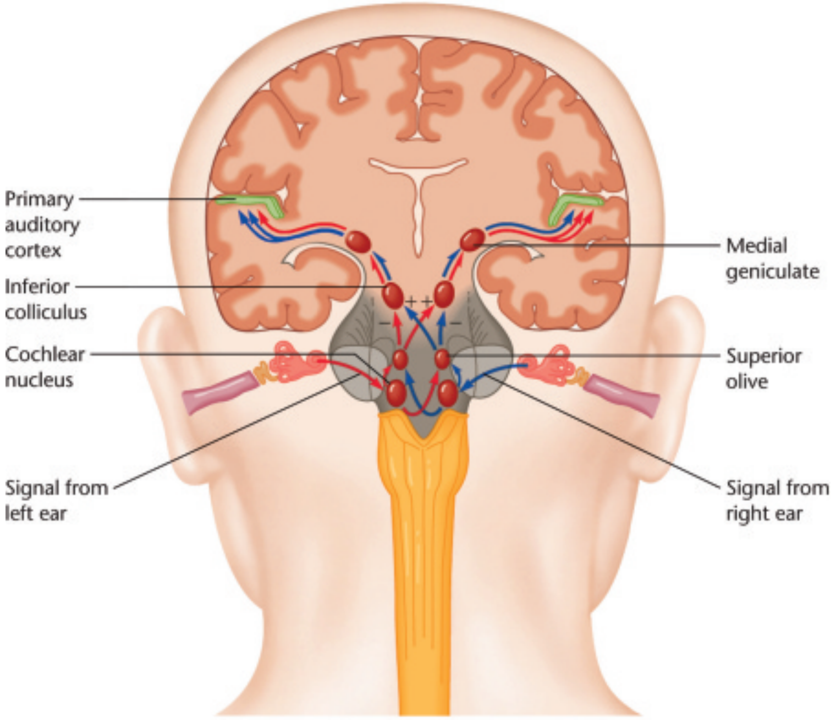
Figure 6.5 Route of auditory impulses from the receptors in the ear to the auditory cortex

The cochlear nucleus receives input from the ipsilateral ear only. All later stages have input from both ears.



The visual and auditory systems differ in this respect: Whereas damage to the primary visual cortex (area V1) leaves someone blind, damage to the primary auditory cortex does not produce deafness. People with damage to the primary auditory cortex have trouble with speech and music, but they identify and localize single sounds reasonably well (Tanaka et al., 1991). The cortex is not necessary for all hearing, but for processing what the information means.

When researchers record from cells in the primary auditory cortex while playing pure tones, they find that most cells have a preferred tone. The auditory cortex provides what researchers call a *tonotopic* map of sounds, as depicted in Figure 6.6. Note that cells responsive to similar frequencies tend to group together. The tonotopic map differs in detail from one person to another (Leaver and Rauschecker, 2016).

Although some cells in the auditory cortex respond well to a single tone, most cells respond best to a complex sound, such as a dominant tone and its harmonics (Barbour and Wang, 2003; Griffiths et al., 2001; Penagos et al., 2004; Wessinger et al., 2001). We experience a tone with harmonics as "richer" than one without them. Surrounding the primary auditory cortex are the secondary auditory cortex and other areas that respond mainly to meaningful sounds, such as animal calls, birdsong, machinery noises, music, and speech (Theunissen and Elie, 2014).

The auditory cortex is important not just for hearing but also for thinking about anything related to hearing. People were asked to look at letter arrays and press a button to indicate whether each array was or was not a real word. The task was easy enough that most people were almost always correct. People with damage to the auditory cortex performed normally, except for words relating to sounds. Not always, but frequently, they might look at something like "thunder" and indicate, "No, that is not a word" (Bonner and Grossman, 2012). That study tells us something about human concepts. If you cannot imagine a sound, then a word relating to sound might seem meaningless.

Stop & Check

4. How is the auditory cortex like the visual cortex?
5. What is one way in which the auditory and visual cortices differ?
6. What evidence suggests that human concepts rely on activating the relevant sensory or motor areas of the cortex?

See pages 196–197 for the answer.

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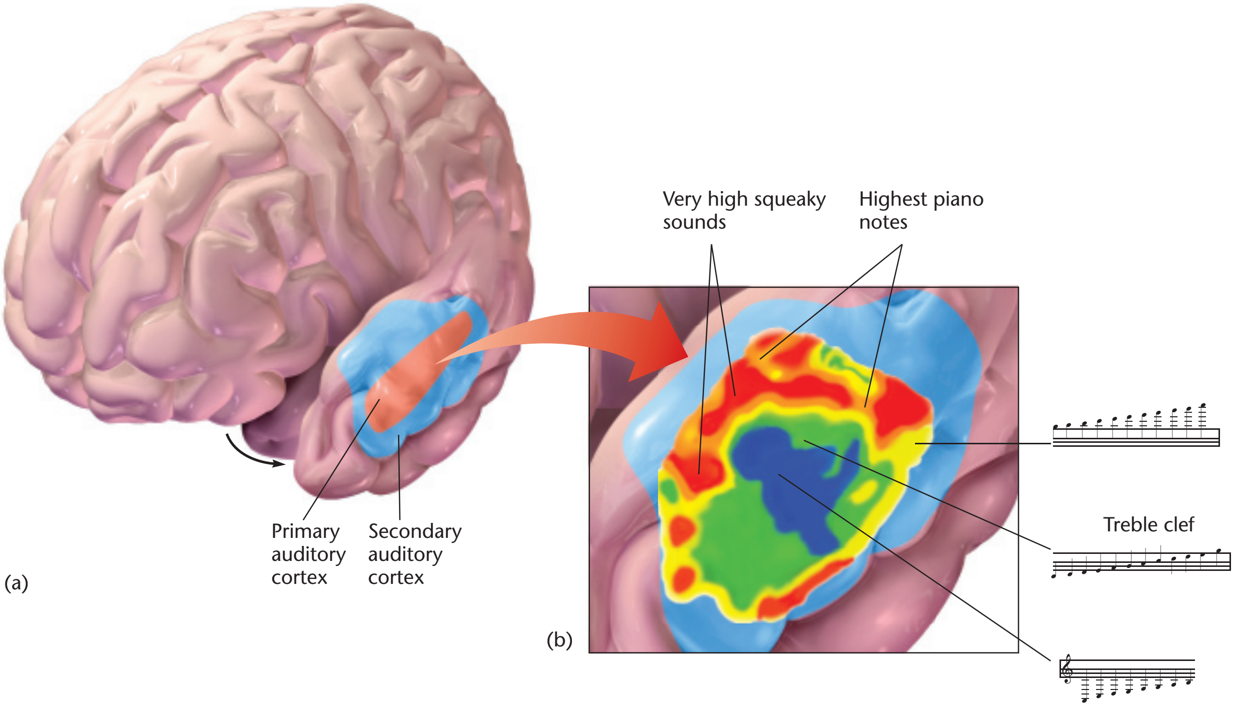
Figure 6.6 The human primary auditory cortex

Cells in each area respond mainly to tones of a particular frequency. Based on the data of Leaver and Rauschecker, 2016.


Very high squeaky sounds
Highest piano notes
Primary auditory cortex
Secondary auditory cortex
(a)
(b)
Treble clef

Sound Localization

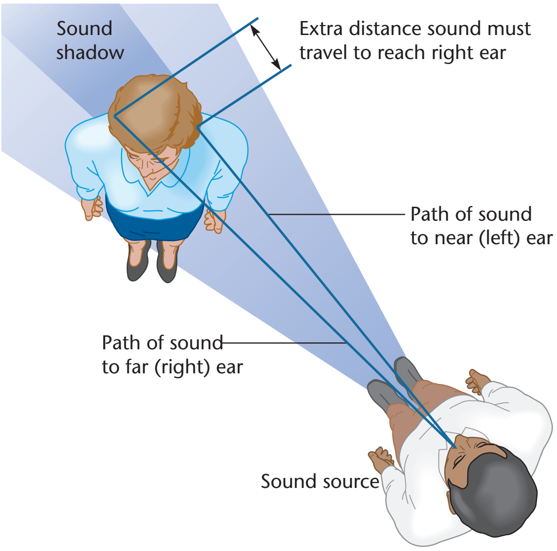
You are walking alone when suddenly you hear a loud noise. You want to know what produced it (friend or foe), but equally, you want to know where it came from. Human sound localization is less accurate than visual localization but nevertheless impressive. Owls localize sounds well enough to capture mice in the dark.

You compare the responses of your two ears to locate a sound. You compare the *times of arrival* at the two ears. A sound coming directly from the side reaches your closer ear about 600 microseconds (μs) before the other (varying by the size of your head). A small difference in arrival times indicates a sound source close to your midline. Time of arrival is useful for localizing sounds with a sudden onset. Most birds' alarm calls increase gradually in loudness, making them difficult for a predator to localize.

You also compare intensity at the two ears. For high-frequency sounds, with a wavelength shorter than the width of the head, the head creates a *sound shadow* (Figure 6.7), making the sound louder for the closer ear. In adult humans, this mechanism produces accurate sound localization for frequencies above 2,000 to 3,000 Hz and less accurate localizations for lower frequencies.

Figure 6.7 Loudness and arrival times as cues for sound localization

Sounds reaching the closer ear arrive sooner as well as louder because the head produces a "sound shadow."


Sound shadow
Extra distance sound must travel to reach right ear
Path of sound to near (left) ear
Path of sound to far (right) ear
Sound source

(**Source:** Based on Lindsay and Norman, 1972)

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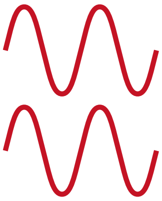
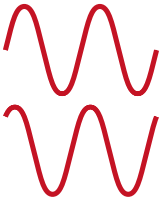
Figure 6.8 Sound waves in phase or out of phase

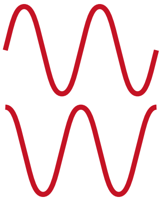
Sound waves that reach the two ears in phase are perceived as coming from directly in front of (or behind) the hearer. The more out of phase the waves, the farther the sound source is from the body's midline.



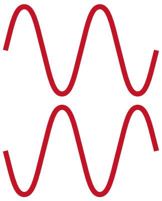
Sound waves in phase



45° out of phase



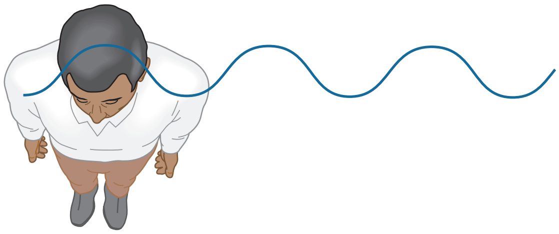
90° out of phase



180° out of phase

Figure 6.9 Phase differences as a cue for sound localization

A sound coming from anywhere other than straight ahead or straight behind reaches the two ears at different phases of the sound wave. The difference in phase is a signal to the sound's direction. With high-frequency sounds, the phases become ambiguous.



You also attend to the *phase difference* between the ears. Figure 6.8 illustrates sound waves that are in phase or out of phase. If a sound originates to the side of the head, the sound wave strikes the two ears out of phase, as illustrated in Figure 6.9. How much out of phase depends on the frequency of the sound, the size of the head, and the direction of the sound. Phase differences provide information that is useful for localizing sounds with frequencies up to about 1500 Hz in humans.

If your head is underwater, you will have trouble localizing low- and medium-frequency sounds. The reason is that sounds travel faster in water than in air, so a sound arrives at the two ears almost simultaneously and the phase differences are also small.

In short, humans localize low frequencies by phase differences and high frequencies by loudness differences. Most can localize a sudden sound of any frequency by the times of onset. All of these methods require learning, because as a human head grows, the distance between ears increases, and humans need to recalibrate how they localize sounds (Kumpik et al., 2010).

Humans can also localize whether a sound is coming from above or below, although less accurately than left vs. right. The pinnae have an irregular shape that filters sound frequencies differently depending on their location up or down, front or back. Humans have to learn to use this information (Trapeau and Schönwiesner, 2018).

Stop & Check

7. Which method of sound localization is more effective for an animal with a small head? Which is more effective for an animal with a large head? Why?

See page 197 for the answer.

Individual Differences

An estimated 4 percent of people have **amusia**, commonly called "tone deafness" (Hyde and Peretz, 2004). Although they are not really unable to hear differences in tones, they do not detect a change less than about the difference between C and C-sharp (Loui et al., 2009). They usually cannot tell whether someone is singing off-key, and they do not detect a "wrong" note in a melody. They also have trouble gauging people's mood, such as happy or sad, from tone of voice (Thompson et al., 2012).

For people with amusia, the auditory cortex appears to approximate a typical structure, but it has fewer than

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average connections to the frontal cortex (Hyde et al., 2007; Loui et al., 2009; Norman-Haignere et al., 2016). The difference is evidently not in hearing itself, but in either memory for pitch (Tillman et al., 2016) or attention to pitch. If you do an Internet search for "amusia test," you can test yourself.

Absolute pitch (or "perfect pitch") is the ability to hear a note and identify it—for example, "That's a B flat." Genetic predisposition contributes (Theusch et al., 2009), but early musical training is also important. Not everyone with musical training develops absolute pitch, but most people with absolute pitch had early musical training (Athos et al., 2007). Absolute pitch is also common among people who speak tonal languages, such as Vietnamese or Mandarin Chinese (Deutsch et al., 2006). In those languages, the meaning of a sound depends on its pitch, and people learn to pay close attention to pitch.

In the traditional manner of testing for absolute pitch, a researcher plays a pure note and asks someone to name it. By that method, only about one person in ten thousand qualifies, and we are tempted to think of absolute pitch as a superpower. However, other methods of testing demonstrate the ability to be more common. Many professional violinists cannot name the pitch of a pure note, but they do better with a violin note. Similar results apply to pianists and presumably people who play other instruments (Wong and Wong, 2014). Nonmusicians cannot name a note, but if they listen to the theme song from a familiar television show, most can determine whether it was played in its usual key or a different one (Schellenberg and Trehub, 2003). The ability to recognize a pitch is common, even if the ability to name it is not.

Deafness

Although few people are totally unable to hear, many people have enough impairment to prevent speech comprehension. The two categories of hearing loss are conductive deafness and nerve deafness.

Diseases, infections, or tumorous bone growth can prevent the bones of the middle ear from transmitting sound waves properly to the cochlea. The result, **conductive deafness** or **middle-ear deafness**, is sometimes temporary. If it persists, it can be corrected by surgery or hearing aids. Because people with conductive deafness have a normal cochlea and auditory nerve, they readily hear their own voices, conducted through the bones of the skull directly to the cochlea, bypassing the middle ear. Because they hear themselves clearly, they may accuse others of talking too softly.

Nerve deafness, or **inner-ear deafness**, results from damage to the cochlea, the hair cells, or the auditory nerve. If it is confined to one part of the cochlea, it impairs hearing of certain frequencies and not others. Nerve deafness can be inherited, it can result from disease, or it can result from exposure to loud noises. Many soldiers, construction workers, and fans of loud rock music expose themselves to noise levels that damage the auditory system (Kujawa and Liberman, 2009).

Tinnitus (tin-EYE-tus or TIN-nit-us) is frequent or constant ringing in the ears. It is common in people who have lost their hearing but rare in people with lifelong deafness. It has many causes (Elgoyhen et al., 2015), but in some cases it resembles phantom limb. Damage to part of the cochlea is like an amputation: If the auditory cortex no longer gets its normal input, other axons invade the deprived area. Some people who have lost their hearing in a particular range report ringing in the ears in the same range, suggesting that something else is activating the vacated synapses. Occasionally, people with hearing loss experience auditory hallucinations, probably because something is stimulating the otherwise inactive synapses (Marschall et al., 2021).

Hearing, Attention, and Old Age

Many older people have hearing problems despite wearing hearing aids. They especially have trouble understanding speech in a noisy room or when someone speaks rapidly. Part of the explanation is that the brain areas responsible for language comprehension have become less active (Peelle et al., 2011). This trend might be just a natural deterioration, or it might be a reaction to prolonged degradation of auditory input. If someone delays getting hearing aids, the language cortex doesn't get its typical input, and it becomes less responsive.

The rest of the explanation relates to filtering out irrelevant sounds. As cochlear hair cells die because of the aging process or anything else, the auditory cortex receives less input than usual. It adjusts by facilitating the excitatory synapses and decreasing the inhibitory synapses, "turning up the volume knob" to increase the sound. That process improves hearing most of the time, but in a noisy environment, it increases the background noise just as much as the conversation. The result is too much competition from irrelevant sounds (Resnik and Polley, 2021). Hearing improves if the listener watches the speaker's face (Golumbic et al., 2013). We all do more lip-reading than we realize.

Stop & Check

8. What evidence suggests that absolute pitch depends on special experiences?
9. Which type of hearing loss—conductive deafness or nerve deafness—would be more common among members of rock bands and why?
10. Why do many older people have trouble hearing in a noisy environment?

See page 197 for the answer.

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Module 6.1 | In Closing

Functions of Hearing

Many people spend much of their day listening to language or music, and we sometimes forget that the original, primary function of hearing has to do with simpler but extremely important issues: What do I hear? Where is it? Is it coming closer? Is it a potential mate, a potential enemy, potential food, or something irrelevant? The organization of the auditory system is well suited to answering these questions.

Summary

1. Sound waves vibrate the tympanic membrane. Three tiny bones convert these vibrations into more forceful vibrations of the smaller oval window, setting in motion the fluid inside the cochlea. Waves of fluid inside the cochlea stimulate the hair cells that send messages to the brain. **188**
2. Humans detect the pitch by two mechanisms. Receptors, or at least volleys of receptors, can fire in synchrony with sound waves, up to about 4,000 Hz. Also, each frequency of sound waves produces a traveling wave that peaks at one point along the basilar membrane. **189**
3. The auditory cortex resembles the visual cortex in many ways. Both have a "what" stream and a "where" or "how" stream. Both are important for imagining sensory stimuli. Both have specialized areas for detecting motion. **191**
4. Each cell in the primary auditory cortex responds best to a particular frequency of tones, although many respond better to complex tones than to a single frequency. **192**
5. Areas bordering the primary auditory cortex respond to more complex sounds and analyze their meaning. The auditory cortex contributes to understanding the meaning of words related to sound. **192**
6. Humans localize high-frequency sounds according to differences in loudness between the ears. We localize low-frequency sounds by differences in phase. If a sound occurs suddenly, we localize it by the times of onset in the two ears. **193**
7. People vary in their hearing, including the possibilities of either amusia or absolute pitch. **194**
8. Deafness may result from damage to the nerve cells or to the bones that conduct sounds to the nerve cells. **195**
9. Many older people have impaired hearing in a noisy environment because the cortex has adjusted to decreased input by facilitating excitatory synapses and decreasing inhibitory ones. **195**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

amplitude **188**
amusia **194**
cochlea **189**
conductive deafness (middle-ear deafness) **195**
frequency **188**
frequency theory **189**
hair cells **189**
nerve deafness (inner-ear deafness) **195**
oval window **189**
pinna **189**
pitch **188**
place theory **190**
primary auditory cortex (area A1) **191**
timbre **189**
tinnitus **195**
tympanic membrane **189**

Thought Question

Why do you suppose that the human auditory system evolved sensitivity to sounds in the range of 20 to 20,000 Hz instead of some other range of frequencies?

Stop & Check Answers

1. Frequency theory.
2. Place theory.
3. Place theory.
4. Any of the following: (a) Both vision and hearing have "what" and "where" pathways. (b) Areas in the superior temporal cortex analyze movement of both visual and auditory stimuli. Damage there can cause motion blindness or motion deafness. (c) The visual cortex is essential for visual imagery, and the primary auditory cortex is essential for auditory imagery. (d) Both the visual and auditory cortices need normal experience early in life to develop normal sensitivities.
5. Damage to the primary visual cortex leaves someone blind, but damage to the primary auditory cortex merely

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impairs perception of complex sounds without making the person deaf.

6. People with damage to the auditory cortex regard many sound-related words, such as "thunder," as if they were nonwords.
7. An animal with a small head localizes sounds mainly by differences in loudness because the ears are not far enough apart for differences in onset time to be very large. An animal with a large head localizes sounds mainly by differences in onset time because its ears are far apart and well suited to noting differences in phase or onset time.
8. Absolute pitch occurs almost entirely among people who had early musical training and is also more common among people who speak tonal languages, which require greater attention to pitch.
9. Nerve deafness is common among rock band members because their frequent exposure to loud noises causes damage to the cells of the ear.
10. When some of the hair cells die, the cortex compensates by facilitating excitatory synapses and decreasing inhibitory synapses, "turning up the volume knob." The result helps hearing in a normal environment, but it increases background sounds in a noisy environment.

Module 6.1 | End-of-Module Quiz

1. When ancient fish evolved into land animals, why did they need to evolve the elaborate mechanisms of the middle ear and inner ear?
   - **a.** To amplify sounds
   - **b.** To localize sounds
   - **c.** To remember sounds
   - **d.** To distinguish among pitches
2. Where are the auditory receptors, known as hair cells?
   - **a.** In the auditory nerve
   - **b.** Along the basilar membrane of the cochlea
   - **c.** Between the incus and the stapes
   - **d.** In the pinna
3. The traveling wave that peaks at a particular point along the basilar membrane enables us to perceive which aspect of a sound?
   - **a.** Loudness
   - **b.** Pitch
   - **c.** Timbre
   - **d.** Location
4. In what way does the auditory cortex resemble the visual cortex?
   - **a.** Both have a special relationship to octaves.
   - **b.** Both respond mainly to stimuli straight in front.
   - **c.** Both have a "what" stream and a "where" or "how" stream.
   - **d.** Both rely on two types of receptors.
5. In what way does the auditory cortex differ from the visual cortex?
   - **a.** The auditory cortex does not respond to movement of a sound source.
   - **b.** Damage to the primary auditory cortex does not cause deafness.
   - **c.** Just imagining a sound does not activate the auditory cortex.
   - **d.** Variations in early experience do not modify the auditory cortex.
6. What type of sound do we localize by comparing the time of arrival at the two ears?
   - **a.** Slow-onset sounds
   - **b.** Sudden sounds
   - **c.** High-frequency sounds
   - **d.** Low-frequency sounds
7. Which structure enables us to localize sounds in the up-down axis?
   - **a.** The basilar membrane
   - **b.** The semicircular canals
   - **c.** The tectorial membrane
   - **d.** The pinna
8. Absolute pitch is more common among what type of people?
   - **a.** People who had a period of auditory deprivation during early childhood
   - **b.** People with extensive musical training in early childhood
   - **c.** People who learned two languages in early childhood
   - **d.** People with older brothers and sisters
9. Why do many older people have trouble understanding speech in a noisy environment?
   - **a.** The auditory cortex is overresponding to background sounds.
   - **b.** The auditory cortex is responding to visual as well as auditory stimuli.
   - **c.** Changes in the corpus callosum have interfered with sound localization.
   - **d.** Loud noises displace the tiny bones connected to the oval window.

Answers: 1a, 2b, 3b, 4c, 5b, 6b, 7d, 8b, 9a.

Module 6.2

The Mechanical Senses

Learning Objectives

After studying this module, you should be able to:

5. Describe the mechanisms of vestibular sensation and somatosensation.
6. Compare physical and emotional pain.
7. Describe methods of relieving pain.

If you place your hand on the surface of your radio, you feel the vibrations that you hear. If you practiced enough, could you learn to "hear" the vibrations with your fingers? Sorry, that won't work. You could detect the beat, but that's about all. If an earless species had enough time, might its vibration detectors evolve into sound detectors? Yes! In fact, our ears did evolve in that way. Much of evolution consists of taking something that evolved for one purpose and modifying it for another purpose.

The *mechanical senses* respond to pressure, bending, or other distortions. They include all the body sensations as well as vestibular sensation, which detects the position and movement of the head. Audition is also a mechanical sense, because hair cells are modified touch receptors. We considered it separately because of its complexity and importance.

Vestibular Sensation

Try It Yourself

Try to read a page while you jiggle your head up and down or back and forth. You can read it easily, unless you jiggle your head too fast. Now hold your head steady and jiggle the page. In that case, you can hardly read it at all. Why?

When you move your head, the vestibular organ adjacent to the cochlea monitors movements and directs compensatory movements of your eyes. When your head moves left, right, up, or down, your eyes move the opposite way, keeping your eyes focused on what you want to see (Brandt, 1991). The vestibular organ cannot help when you wiggle the page.

Sensations from the vestibular organ detect the tilt of the head and the head's acceleration. You use that information to guide eye movements and maintain balance. Mice with an impairment of vestibular sensation frequently lose their balance. They cannot swim or float because they are often upside-down (Mariño et al., 2010). People with impairments of the vestibular system stagger and fall.

The vestibular organ, depicted in Figure 6.10, consists of the *saccule*, *utricle*, and three semicircular canals. Like the hearing receptors, the vestibular receptors are modified touch receptors. Calcium carbonate particles called *otoliths* lie next to the hair cells. When the head tilts, the otoliths push against hair cells and excite them, telling the brain the direction of tilt. When you move, the otoliths tell the brain which direction you are moving.

The three **semicircular canals**, oriented in perpendicular planes, are filled with a fluid and lined with hair cells. Acceleration of the head at any angle causes the fluid in one of these canals to move, just as the water in a bucket will splash if you jerk the bucket from side to side. The fluid then pushes against the hair cells in the semicircular canals, setting up action potentials. Unlike the saccule and utricle, the semicircular canals record only the rate of acceleration, not the position of the head at rest. They are also insensitive to sustained motion. If you start forward on a bicycle or other vehicle, the semicircular canals respond as you accelerate, but they stop when you keep a steady pace.

The vestibular organ is nearly the same size for all mammalian species. Whales are 10 million times as massive as mice, but their vestibular organ is only 5 times as large (Squires, 2004). Evidently a small vestibular organ provides all the information we need.

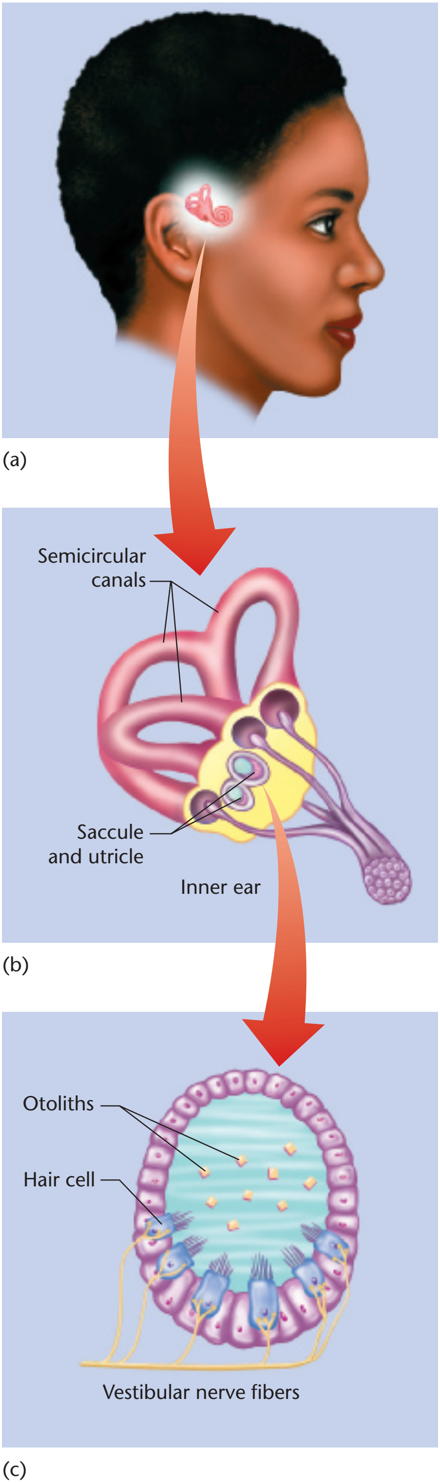
Stop & Check

11. People with damage to the vestibular system have trouble reading street signs while walking. Why?

See page 209 for the answer.

Figure 6.10 Structures for vestibular sensation

(a) Location of the vestibular organs. (b) Structures of the vestibular organs. (c) Cross-section through a utricle. Calcium carbonate particles, called otoliths, press against different hair cells depending on the tilt and acceleration of the head.



Somatosensation

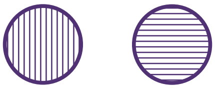
The **somatosensory system**, the sensation of the body and its movements, is not one sense but many, including touch, deep pressure, the position and movement of joints, pain, and temperature.

Somatosensory Receptors

Table 6.1 describes somatosensory receptors, including those depicted in Figure 6.11 (Handler and Ginty, 2021; Kim and Lee). Other receptors not in the table respond to joint movement or muscle movements.

Consider the **Pacinian corpuscle**, which detects vibrations or sudden displacements on the skin (Figure 6.12). On the inside is the neuron membrane. The onion-like outer structure provides mechanical support that resists gradual or constant pressure, insulating the neuron against most touch stimuli. Only a sudden or vibrating stimulus bends the membrane, enabling sodium ions to enter and start an action potential (Loewenstein, 1960).

Suppose you feel objects with thin grooves like these, without looking at them, and try to feel whether the grooves go left to right or up and down:



The experimenter varies the width of the grooves to find the narrowest grooves you can discern. On average, women can detect grooves about 1.4 mm apart, whereas men need the grooves to be about 1.6 mm apart. Your first question might be, "Who cares?" but if you get past that question, your second question might be *why* males and females differ. Unlike many male-female differences, this one is easy to explain. On average, females have smaller

Table 6.1 | Somatosensory Receptors and Probable Functions

Receptor	Location	Responds to:
Free nerve ending	Any skin area	Pain and temperature
Hair-follicle receptors	Hair-covered skin	Movement of hairs, skin stroke
Meissner's corpuscles	Hairless areas, mainly fingertips	Discriminative touch and vibration
Pacinian corpuscles	Any skin area	Vibration or sudden touch
Merkel's disks	Any skin area	Light touch
Ruffini endings	Any skin area, but scarce in humans	Skin stretch, roughness
Krause end bulbs	Mostly hairless areas	Uncertain

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Figure 6.11 Sensory receptors in the skin

The receptors respond to several types of skin sensation, as described in Table 6.1.

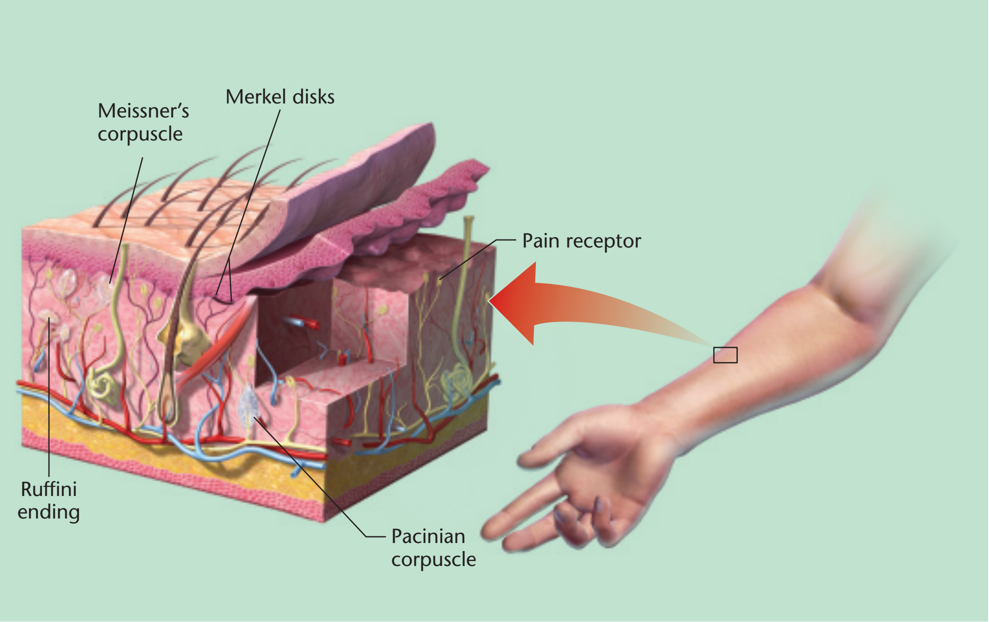
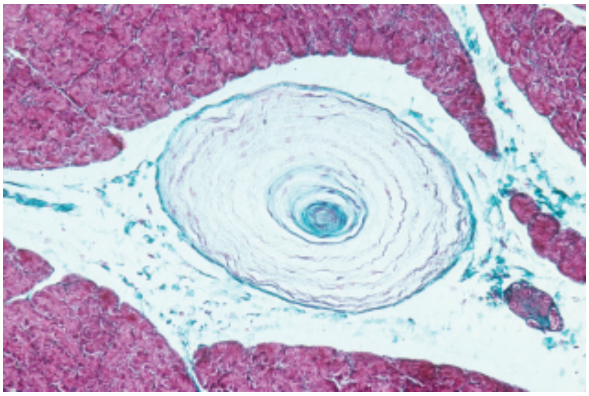


Figure 6.12 A Pacinian corpuscle

Pacinian corpuscles are receptors that respond best to sudden displacement of the skin or to high-frequency vibrations. The onion-like outer structure provides a mechanical support so that only a sudden stimulus can bend the neuron membrane.


M. I. Walker/Science Source

(**Source:** Ed Reschke)

fingers. They have the same number of Merkel disks and Meissner's corpuscles as males, but compacted into a smaller area. People with the same size fingers have the same touch sensitivity (Peters et al., 2009).

The body has receptors for temperature, a critical variable because overheating or overcooling the body can be fatal. The systems for cooling and heating display an interesting asymmetry: Cold-sensitive neurons in the spinal cord exhibit little response to a constant low temperature, but they respond to a drop in temperature. A cell that responds to a drop from 39° C to 33° C would also respond to a drop from 33° C to 27° C. Thus, on a very hot day, you might detect a breeze as "cool," even though the air in the breeze is fairly warm. In contrast, heat-sensitive neurons in the spinal cord respond to the absolute temperature, and they do not adapt. A cell that responds to 44° C will respond the same way regardless of whether the skin was hotter, cooler, or the same temperature a minute or two ago (Ran et al., 2016).

Our temperature receptors also respond to certain chemical stimuli. **Capsaicin**, found in jalapeños and other hot peppers, stimulates the receptors for painful heat (Caterina et al., 1997). Capsaicin can produce burning or stinging sensations on many parts of your body, as you may have experienced if you ever touched the insides of hot peppers and then rubbed your eyes. Szechuan peppers also stimulate the heat receptors, and in addition stimulate receptors that give a tingling sensation (Bautista et al., 2008). Menthol and mint stimulate the coolness receptor (McKemy et al., 2002).

Stop & Check

12. How do jalapeños produce a hot sensation?

See page 209 for the answer.

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Tickle

The sensation of tickle is interesting but poorly understood. Why does it exist at all? Why do you laugh if someone fingers your armpit? Chimpanzees respond to similar sensations with bursts of panting that resemble laughter. And yet tickling is unlike humor. Most people love humor, but most people don't like being tickled, at least not for long. Laughing at a joke makes you more likely to laugh at the next joke, but laughing after being tickled doesn't change your likelihood of laughing at a joke (C. R. Harris, 1999).

Why can't you tickle yourself? It is for the same reason that you cannot surprise yourself. Your expectation of the stimulus weakens your response to it (Blakemore et al., 1998). Actually, some people can tickle themselves—a little—if they tickle the right side of the body with the left hand or the left side with the right hand. You might also be able to tickle yourself as soon as you wake up, before your brain is fully aroused. Try that some time when you awaken.

Try It Yourself

Somatosensation in the Central Nervous System

Information from touch receptors in the head enters the central nervous system through the cranial nerves. Information from receptors below the head enters through the 31 spinal nerves (Figure 6.13). Each spinal nerve has a sensory component and a motor component.

Each spinal nerve *innervates* (connects to) a limited area of the body called a **dermatome** (Figure 6.14). For example, the third thoracic nerve (T3) innervates a strip of skin just above the nipples as well as the underarm area. The borders between dermatomes are less distinct than Figure 6.14 implies. Each dermatome overlaps one-third to one-half of the next dermatome.

Various types of somatosensory information—such as touch, pressure, and pain—travel through the spinal cord in separate pathways toward the thalamus, which then sends impulses to different areas of the primary somatosensory cortex in the parietal lobe. Information from skin sensations also goes to the anterior cingulate cortex (Figure 3.10) and insular cortex, which respond to the pleasantness or unpleasantness of the sensation (Case et al., 2016).

Two parallel strips along the somatosensory cortex respond mostly to touch on the skin. Two other parallel strips respond mostly to deep pressure and movement of the joints and muscles (Kaas, 1983). In short, various aspects of body sensation remain mostly separate all the way to the cortex. Along each strip of somatosensory cortex, each subarea responds to an area of the body, as exhibited in Figure 3.23.

The primary somatosensory cortex, **S1**, is essential for touch experiences. When the fingers touch something, people are conscious of only those that produce enough arousal in the primary somatosensory cortex (Palva et al., 2005). If someone touches you quickly on two nearby points on the hand, you will have an illusory experience of a single touch midway between those two points. When that happens, the activity in the primary somatosensory cortex corresponds to that midway point (Chen et al., 2003). In other words, the activity in S1 matches what you experience.

Damage to the somatosensory cortex impairs body perceptions. A patient with damage to her somatosensory cortex had trouble putting her clothes on correctly. Also she could not point correctly in response to such directions as "show me your elbow," although she did point correctly

Figure 6.13 The human central nervous system (CNS)

Spinal nerves from each segment of the spinal cord exit through the correspondingly numbered opening between vertebrae.

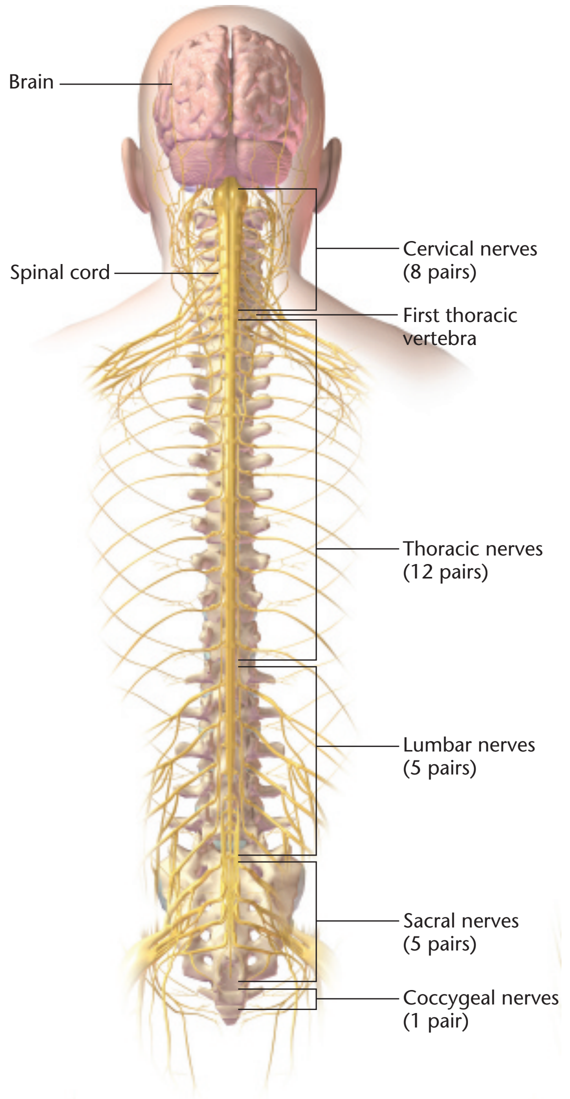

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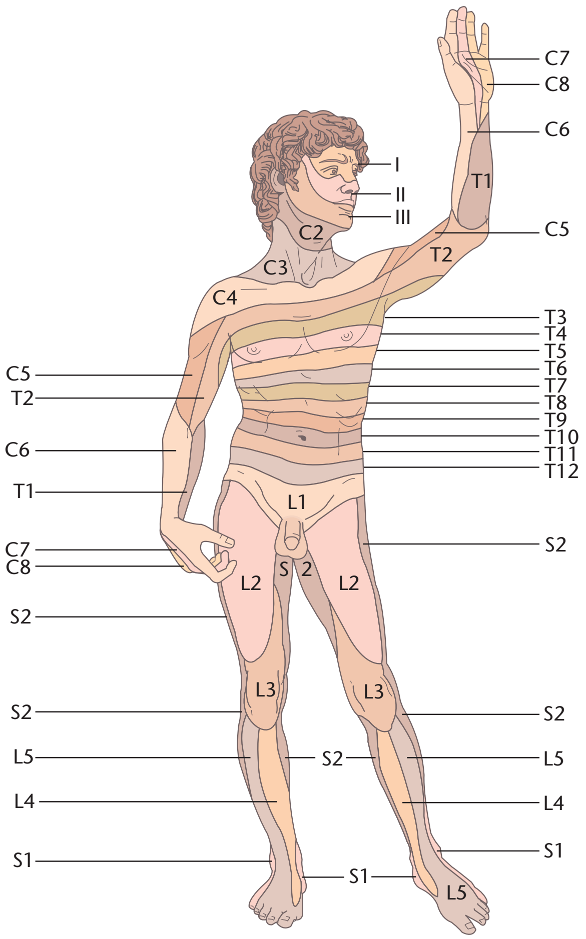
Figure 6.14 Dermatomes innervated by the 31 sensory spinal nerves

Areas I, II, and III of the face are not innervated by the spinal nerves but instead by three branches of the fifth cranial nerve. Although this figure exhibits distinct borders, the dermatomes overlap one another by about one-third to one-half of their width.



to objects in the room. When told to touch her elbow, her most frequent response was to feel her wrist and arm and suggest that the elbow was probably around there, somewhere (Sirigu et al., 1991).

One patient had an illness that destroyed the myelinated somatosensory axons from below his nose but spared his unmyelinated axons. He still felt temperature, pain, and itch, because they depend on the unmyelinated axons. However, he had no conscious perception of touch, which depends on myelinated axons. Curiously, if someone lightly stroked his skin, he experienced a vague sense of pleasure. Recordings from his brain indicated no arousal of his primary somatosensory cortex but increased activity in the insular cortex, which responds to the emotional events and many aspects of self-awareness (Björnsdotter et al., 2009). Evidently, unmyelinated axons conveyed enough activity to the insular cortex to produce the emotional aspect of touch even though he had no conscious sensation of the touch itself.

Remember blindsight? A similar phenomenon occurs for touch, known as **numbsense**. When the primary sensory cortex (S1) is inactive, either because of damage or because of temporary suppression, some people correctly "guess" the location of a touch while insisting that they did not consciously feel it. This phenomenon is highly variable, as some people are almost always accurate and others do no better than chance (Ro and Koenig, 2021). When it occurs, the likely explanation is that the thalamus sends enough input to areas surrounding S1 for location identification, but not enough for conscious perception.

Stop & Check

13. How is S1 similar to V1?
14. What evidence suggests that the primary somatosensory cortex (S1) is essential for conscious touch perception?
15. How do the responses to skin sensations differ between the somatosensory cortex and the insular cortex or the anterior cingulate cortex?

See page 209 for the answer.

Pain

Pain and depression are closely linked. People in pain become depressed and unmotivated. People who are depressed become more sensitive to pain. Economic insecurity leads to depression and makes a pain feel worse (Chou et al., 2016). Some languages use the same word to mean either "sick" or "depressed."

Depression is more common in women than in men, and women tend to experience more pain than men (Bimpong et al., 2021). That difference raises a serious point. Much of the biological research on pain has relied on just males—sometimes humans, sometimes rodents. The reasoning was that females were assumed to be more variable, because of their hormonal cycles. That assumption is wrong as a general rule. Still, regardless of variability, if males and females react the same way, then using just one sex or the other makes no difference. The problem is, males and females do not react the same way to pain. Activating certain neurons in the midbrain decreases pain sensitivity in male mice, but not in females (Yu et al., 2021). The pain-relieving effects of opiates and cannabinoids differ between males and females (Blanton et al., 2021; Mogil, 2020). Researchers are beginning to pay more attention to male-female differences in pain, but that research emphasis is overdue.

Stimuli and Spinal Cord Paths

Pain begins with the least specialized of all receptors, a bare nerve ending (Figure 6.11). Because the axons carrying pain information are thin with little or no myelin,

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they conduct impulses relatively slowly, in the range of 2 to 20 meters per second (m/s). The thicker and faster axons convey sharp pain, whereas the thinner ones convey duller pain, such as postsurgical pain. Mild pain releases the neurotransmitter glutamate, whereas stronger pain releases both glutamate and neuropeptides, including substance P and CGRP (calcitonin gene-related peptide).

In the spinal cord, one path conveys pain and temperature sensations, and a second path conveys touch. The two paths differ in a way that Figure 6.15 illustrates: The pain/temperature pathway crosses immediately from receptors to a tract on the contralateral side of the spinal cord. Touch information travels up the ipsilateral side of the spinal cord to the medulla, and then crosses to the contralateral side. Consider what happens to pain and touch if someone receives a cut that goes halfway through the spinal cord. You can reason out the answer in the next Stop and Check question.

Input from the pain/temperature pathway to the thalamus and then to the somatosensory cortex reports the intensity and location of the pain. Input to the hypothalamus, amygdala, and anterior cingulate cortex pertains to the unpleasant emotional aspect (Hunt and Mantyh, 2001; Figure 6.16). After damage to the somatosensory cortex, people have trouble localizing the pain. After damage to the amygdala, people localize the pain, but they do not feel it as unpleasant and they take no steps to avoid it (Corder et al., 2019; Foltz and White, 1962). The emotion-relevant areas react not only to feeling your own pain but to watching someone else in pain, especially someone you care about (Corradi-Dell'Acqua et al., 2011; Singer et al., 2004).

Stop & Check

16. Suppose your spinal cord is cut on the right side only. For the part of the body below that cut, will you lose pain sensation on the left side or the right side? Will you lose touch sensation on the left side or the right side?
17. After a hypnotic suggestion to feel no pain, people sometimes continue to describe their pain, but they seem indifferent to it (Rainville et al., 1997). What does this observation imply about the brain mechanisms?

See page 209 for the answer.

Emotional Pain

Sometimes you say that someone hurt your feelings. After a relationship breakup, you might say you feel emotional pain. Are these just an expression, or is emotional distress really like pain?

Hurt feelings do resemble physical pain. Imagine yourself in this experiment: You sit in front of a computer screen, playing a virtual ball-tossing game with two people your own age. You "catch" a ball and then "throw" it to one

Figure 6.15 Spinal pathways for touch and pain

Pain information crosses to the contralateral side of the spinal cord at once, whereas touch information does not cross until the medulla.

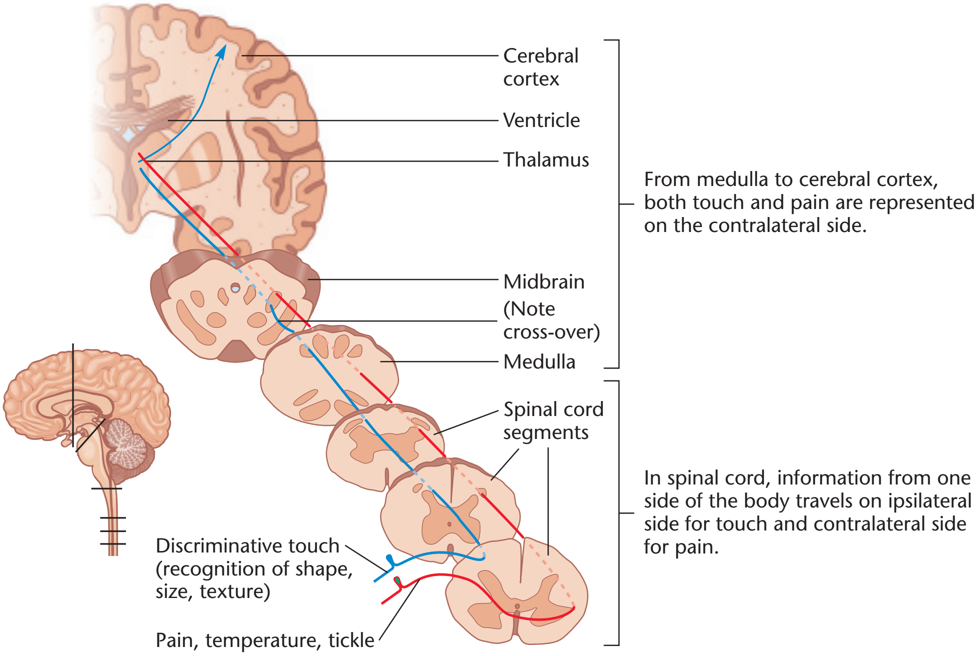
Cerebral cortex
Ventricle
Thalamus
From medulla to cerebral cortex, both touch and pain are represented on the contralateral side.
Midbrain
(Note cross-over)
Medulla
Spinal cord segments
In spinal cord, information from one side of the body travels on ipsilateral side for touch and contralateral side for pain.
Discriminative touch (recognition of shape, size, texture)
Pain, temperature, tickle

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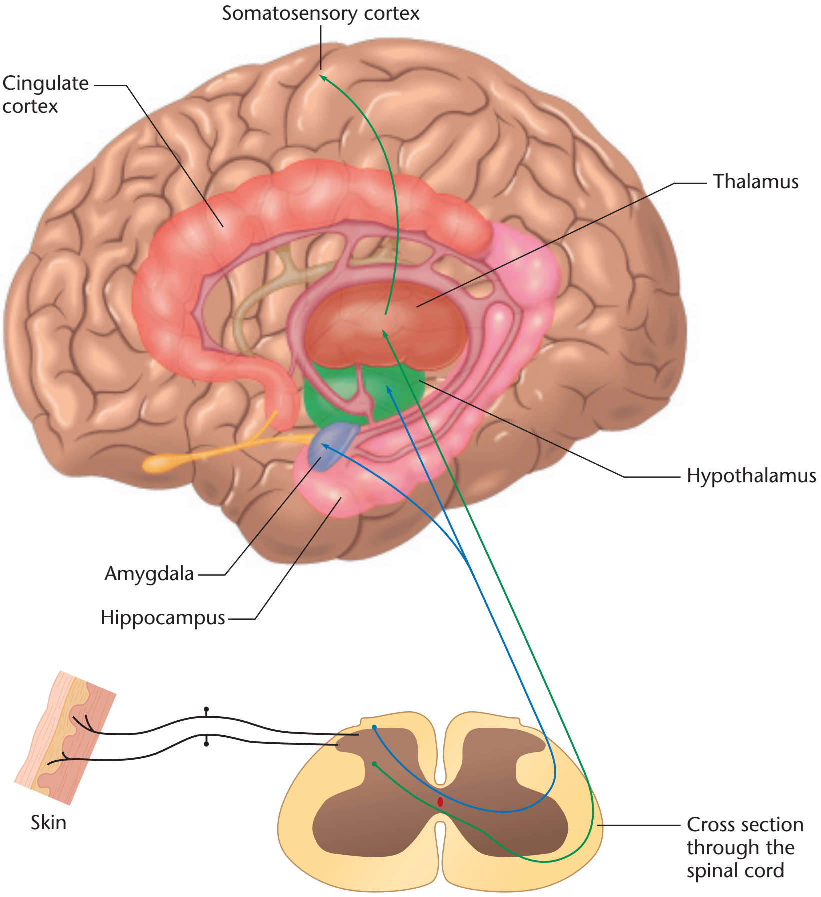
Figure 6.16 Pain messages in the human brain

A pathway to the thalamus, and from there to the somatosensory cortex, conveys the sensory aspects of pain. A separate pathway to the hypothalamus, amygdala, and cingulate cortex produces the emotional aspects.



(**Source:** Hunt and Mantyh, 2001)

of the others, who then tosses it back to someone. Unbeknownst to you, the other two have been paid to play certain roles. At first, they throw it to you a fair share of times, but before long they start passing it back and forth between the two of them, leaving you out. Not much is at stake here—you don't even know these people, and playing catch with an imaginary ball is one of the silliest video games ever, so who cares, right?—but the experience reminds you of all the hurtful times in your life when people ignored you. Experimenters monitored people's brain activity during this virtual ball-throwing task and found increased activity in the cingulate cortex, an area responsive to the emotional aspects of pain (Eisenberger et al., 2003). Later studies found that this type of social exclusion does not always activate pain areas, but it often activates areas associated with evaluating others' actions—that is, "why are they acting this way?" (Mwilambwe-Tshilobo and Spreng, 2021). A study with more intense hurt feelings, based on remembering a recent romantic breakup, while looking at a photo of the ex-boyfriend or girlfriend, activated not only the cingulate cortex but also the sensory areas responsive to physical pain (Kross et al., 2011).

Hurt feelings are like real pain in another way: You can relieve hurt feelings with pain-relieving drugs such as acetaminophen (Tylenol®)! Researchers repeated the virtual ball-tossing study, but they gave some people acetaminophen and others a placebo. Those taking acetaminophen exhibited less response in the cingulate cortex and other emotionally responsive areas. The researchers also asked college students to keep daily records about hurt feelings and social pain, while some took daily acetaminophen pills and others took a placebo. Those taking acetaminophen reported fewer cases of hurt feelings, and the frequency of hurt feelings declined over days as they continued taking the pills (De Wall et al., 2010). The next time someone says you hurt their feelings, you could tell them to quit complaining and take a Tylenol. However, there is a price to pay: People taking acetaminophen also

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decrease their evaluations of positive experiences (Durso et al., 2015). Evidently it blunts both good and bad emotional experiences.

Ways of Relieving Pain

Pain evolved for a reason. People with a genetic inability to feel pain do not know when they are getting hurt (Dib-Hajj et al., 2015). One boy with this condition performed street theater in Pakistan by thrusting a knife through his arm or walking on burning coals. He died at age 14 (Cox et al., 2006). Still, although you wouldn't want to eliminate pain, it is good to control it.

Opioids and Endorphins

After pain alerts you to an injury, you do not need constant reminders, at least not of the same intensity. The brain puts the brakes on prolonged pain by **opioid mechanisms**—systems that respond to opiate drugs and similar chemicals. Candace Pert and Solomon Snyder (1973) discovered that opiates bind to receptors in the spinal cord and the **periaqueductal gray area** of the midbrain (Figures 6.17 and 6.18).

The discovery of opiate receptors was important because it revealed that opiates act on the nervous system rather than the injured tissue. Furthermore, it implied that the nervous system has its own opiate-type chemicals. The transmitters that attach to the same receptors as morphine are known as **endorphins**—a contraction of *endo*genous mor*phines*. The brain produces several types of endorphins, which relieve different types of pain, such as the pain from a cut versus the pain from a burn (Scherrer et al., 2009).

Inescapable pain is especially potent at stimulating endorphins and inhibiting further pain (Sutton et al., 1997). Presumably, the evolutionary function is that continued intense pain accomplishes nothing when you already know about the problem and escape is impossible. Endorphins are also released during intense pleasures, such as orgasm and when you listen to thrilling music that sends a chill down your spine (A. Goldstein, 1980). Those experiences tend to decrease pain.

Morphine does not affect large-diameter axons that convey sharp pain. For that reason, morphine is ineffective against the sharp pain of a surgeon's knife. However, morphine does block messages from thinner axons that convey slow, dull pain such as postsurgical pain (Taddese et al., 1995).

Figure 6.17 Synapses for pain and its inhibition

A neuron releases endorphins at presynaptic synapses, thereby inhibiting a cell conveying pain sensations.

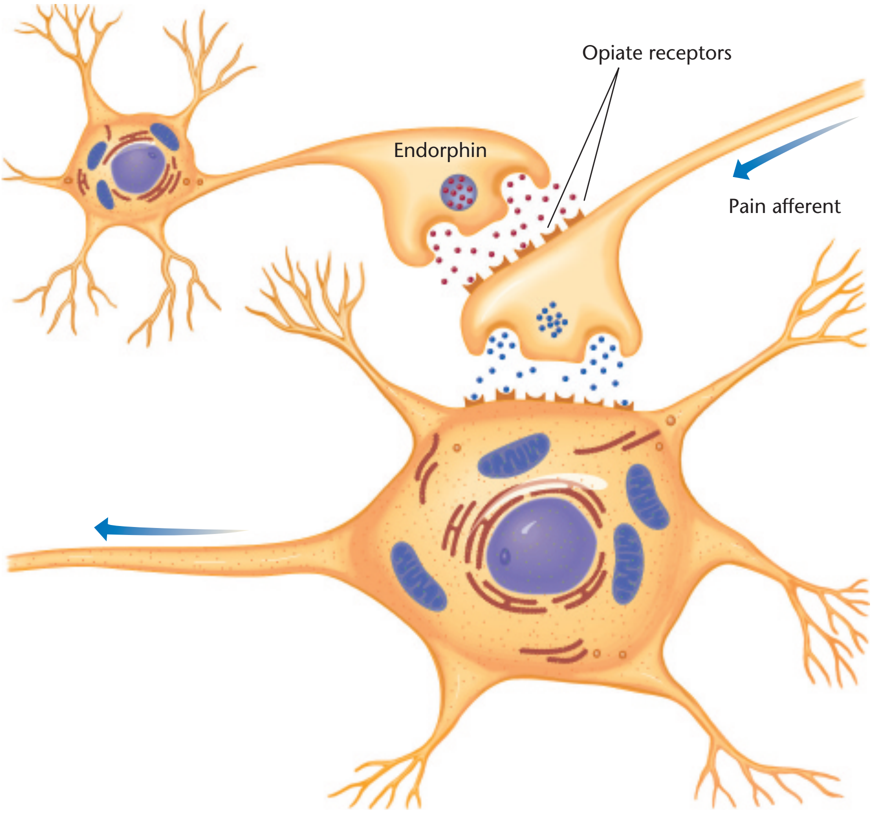

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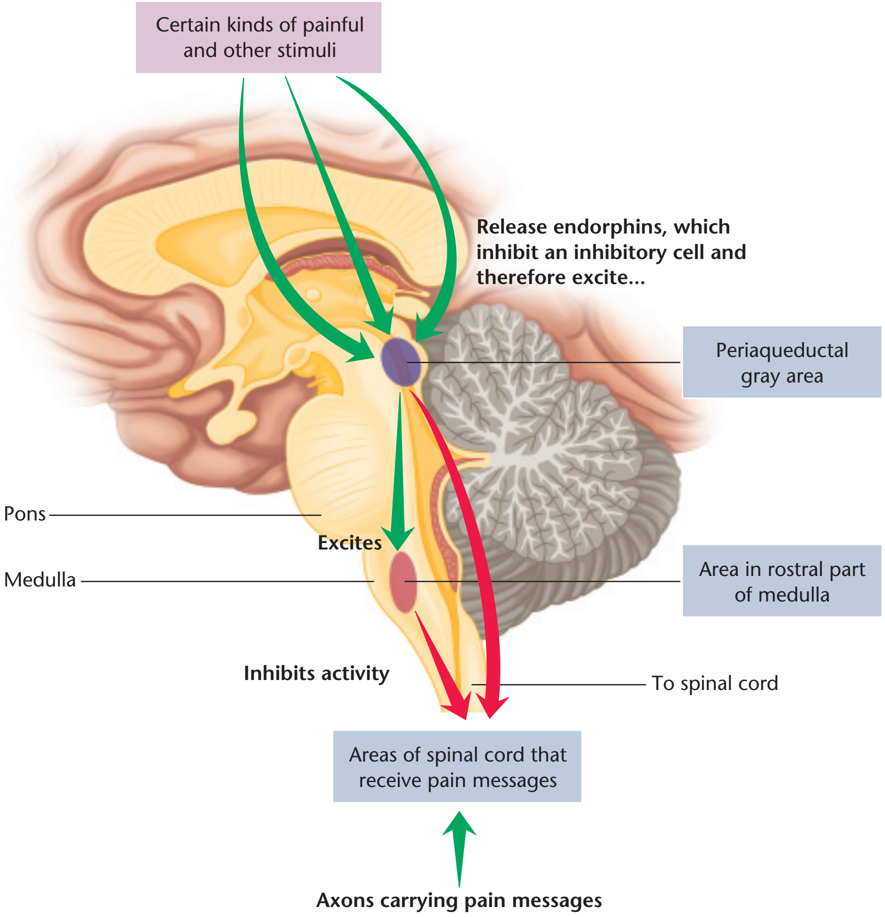
Figure 6.18 The periaqueductal gray area, where electrical stimulation relieves pain

Periaqueductal means "around the aqueduct," a passageway of cerebrospinal fluid between the third and fourth ventricles.


Certain kinds of painful and other stimuli
Release endorphins, which inhibit an inhibitory cell and therefore excite...
Periaqueductal gray area
Pons
Excites
Medulla
Area in rostral part of medulla
Inhibits activity
To spinal cord
Areas of spinal cord that receive pain messages
Axons carrying pain messages

Morphine and other opiates are effective pain reducers, but they have limitations. Anything that causes pain increases the breathing rate, and the opiates that decrease pain also decrease breathing, with potentially fatal consequences (Liu et al., 2022). Opiate drugs produce unwanted effects including sedation, nausea, and constipation. Prolonged use of morphine can alter the immune system, sometimes causing a extended *increase* in pain (Grace et al., 2016).

Other Ways to Relieve Pain

Gate theory, proposed decades ago (Melzack and Wall, 1965), was an attempt to explain why some people withstand pain better than others, and why the same injury hurts worse at some times than others. According to gate theory, spinal cord neurons that receive messages from pain receptors also receive input from other inputs that can close the gates for the pain messages. You may have noticed that when you have an injury, you can decrease the pain by gently rubbing the skin around it or by concentrating on something else. The input from gentle touch or top-down influences from the prefrontal cortex inhibits the pain messages in the spinal cord.

Given the difficulties with opiate drugs, researchers search for other types of medication. Unfortunately, most animal research has focused on injury-related pain, instead of the long-term pains that cause the greatest problems for people (Ma, 2022). Cannabinoids—chemicals found in marijuana—relieve certain kinds of pain. Cannabinoids act in the periphery of the body as well as the CNS (Agarwal et al., 2007). They reduce inflammation and inhibit the release of glutamate and GABA. Despite much public enthusiasm for the pain-relieving potential of cannabinoids, high-quality research on this topic so far has been sparse.

Cannabinoids have demonstrated promise for treating **neuropathic pain**, a condition of chronic pain that lasts long after the original cause of pain has ended (Wolf et al., 2020). Damaged tissue releases histamine, nerve growth

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factor, and other chemicals that help repair the damage but also magnify the responses of nearby heat and pain receptors (Chuang et al., 2001; Devor, 1996; Tominaga et al., 1998). Neuropathic pain occurs for another reason also: After injury to sensory neurons, most of the axons from touch receptors fail to regenerate. Pain axons produce collateral sprouts that take over receptors previously sensitive to touch, such as Meissner's corpuscles. From then on, even light touch stimulates pain messages (Gangadharan et al., 2022). Neuropathic pain is difficult to treat, and therefore any benefit from cannabinoids is encouraging.

Another approach for pain relief uses capsaicin, a chemical in jalapeños and other hot peppers. Wearing a skin patch with a high concentration of capsaicin for an hour produces a temporary burning sensation, but it causes an excessive buildup of calcium in the heat and pain neurons, and it damages those neurons' mitochondria, rendering the cells nonfunctional until they regenerate over the next three to five months (Anand and Bley, 2011; Arora et al., 2021).

Do not try eating hot peppers to reduce pain in, say, your legs. The capsaicin you eat passes through the digestive system without entering the blood. Eating it will not relieve your pain, unless the pain happens to be in your tongue (Karrer and Bartoshuk, 1991).

Another possibility for the future: Remember the voltage-gated sodium channels responsible for the action potential. The nervous system has nine types of voltage-gated sodium channels, and type number 7, abbreviated as Nav1.7, is especially important for axons conveying pain and olfactory sensations. People with a mutation that interferes with this sodium channel are almost completely insensitive to pain, and also to most odors. Researchers developed drugs to block Nav1.7 in hopes of helping people with chronic pain. Unfortunately, the results so far have been disappointing, because the drugs they developed do not cross the blood-brain barrier. A drug blocking Nav1.7 could be effective, but only if it crosses the blood-brain barrier (Goodwin and McMahon, 2021; MacDonald et al., 2021).

Stop & Check

18. Why do opiates relieve dull pain but not sharp pain?
19. What causes neuropathic pain?
20. Why is sodium channel Nav1.7 interesting to pain researchers?

See page 209 for the answer.

Placebos

In much medical research, an experimental group receives a potentially active treatment and the control group receives a **placebo**, a drug or other procedure with no pharmacological effects. Placebos have little influence on most illnesses, but they often relieve pain, depression, and anxiety (Hróbjartsson and Gøtzsche, 2001; Wager and Atlas, 2015). People who receive placebos do not just *say* the pain decreased; scans of the brain and spinal cord also exhibit a decreased response (Eippert et al., 2009). Placebos produce their greatest effect on the emotional response to pain, as recorded in the cingulate cortex (Petrovic et al., 2002; Wager, Scott, and Zubieta, 2007). They also reduce the emotional response to watching someone else in pain (Rütgen et al., 2015). Oddly, placebos can reduce pain even when people know they are receiving a placebo (Rosenzweig, 2016). Conversely, if someone expects an unpleasant reaction to a drug, the nervous system increases that response also—a **nocebo** effect, the opposite of placebo (Geuter and Büchel, 2013; Koban and Wager, 2016). Expectations are important. Increasing the price of a drug can increase either its placebo or its nocebo effect (Tinnerman et al., 2017).

Relaxation is not the whole explanation for placebo effects. In one study, people were given painful injections into their hands and feet. They were also given a placebo cream on one hand or foot and told that it was a powerful painkiller. People reported decreased pain in the area that got the placebo but normal pain on the other three extremities (Benedetti et al., 1999). If placebos were simply producing relaxation, it should have affected all four extremities. Distraction is not the whole explanation, either. Distraction plus placebo relieves pain more than distraction alone does (Buhle et al., 2012). A placebo increases activity in parts of the prefrontal cortex, suggesting that a placebo exerts its effects by top-down control of sensations and emotions (Meyer et al., 2015).

Stop & Check

21. Which aspect of pain is most responsive to relief by placebos?

See page 209 for the answer.

Itch

Have you ever wondered, "What is itch, anyway? Is it a kind of pain? A kind of touch? Or something else altogether?" The answer is that itch is a separate sensation. Researchers identified special receptors for itch (Y.-G. Sun et al., 2009) and a special peptide that itch releases in the nervous system (Chen, 2021).

You have two causes of itch (Sakai and Akiyama, 2020). If an insect crawls slowly across your skin, that is one cause of itch. Just imagining it might make you itch right now. You can get the same type of itch by lightly rubbing rough leaves against your skin. The other cause is tissue damage, such as when your skin is healing after a cut. Your skin releases histamines that dilate blood vessels and produce an itching sensation. Antihistamines relieve this type of itch, but not the itch you get from something crawling over your skin. The two types of itch sensation travel in parallel paths to the brain.

Itch receptors respond slowly, and when they do, their axons transmit impulses at only half a meter per second. At that rate, an action potential from your foot needs 3 or 4 seconds to reach your head. You might try lightly rubbing some rough leaves against your ankle. (You could get an insect to crawl across your ankle, but you probably don't want to.) Note how soon you feel the touch sensation and how much more slowly you notice the itch.

Try It Yourself

Itch is useful because it directs you to scratch the itchy area and remove whatever is irritating your skin. Your brain is not satisfied until you scratch hard enough to produce mild pain, because pain inhibits itch (Davidson et al., 2009). Opiates, which decrease pain, increase itch (Andrew and Craig, 2001; Y. Liu et al., 2010; Moser and Giesler, 2013). The inhibitory relationship between pain and itch is clear evidence that itch is not a type of pain. Further evidence is the demonstration that blocking itch fibers does not reduce pain (Roberson et al., 2013).

This research helps explain an experience that you may have noticed. When a dentist gives you Novocain before drilling a tooth, part of your face becomes numb. An hour or more later, as the drug's effects start to wear off, you may feel an itchy sensation in the numb portion of your face. But when you try to scratch it, you feel nothing because the touch and pain sensations are still numb. Evidently, the effects of Novocain wear off faster for itch than for touch and pain. The fact that you can feel itch at this time demonstrates that it is not just a form of touch or pain. Scratching the partly numb skin does not relieve the itch. Evidently, scratching has to produce some pain to decrease the itch.

Stop & Check

22. Do opiates increase or decrease itch sensations?

See page 209 for the answer.

Module 6.2 | In Closing

The Mechanical Senses

You have learned that pain messages go to both the brain's touch area (somatosensory cortex) and its emotion area (amygdala and related structures). The same is true for temperature and touch. The body senses provide us with information, and they are also an important source of pleasure or displeasure.

Summary

1. The vestibular system detects the position and acceleration of the head and adjusts body posture and eye movements accordingly. **198**
2. The somatosensory system detects stimulation of the skin and internal tissues. **199**
3. The brain maintains parallel somatosensory representations of the body. **201**
4. Activity in the primary somatosensory cortex corresponds to the experience, even if it is illusory. **201**
5. Painful information takes two routes to the brain. A route to the somatosensory cortex conveys information about intensity and location. A route to the anterior cingulate cortex and related areas conveys the emotional aspect. **202**
6. Opiate drugs attach to endorphin receptors. Endorphins decrease pain by blocking activity of pain neurons. **205**
7. Morphine combats pain, but excessive or repeated use poses serious risks. Cannabinoids and capsaicin are among the alternative ways to relieve pain. **205**
8. Pain can increase or decrease depending on other stimuli and expectations. According to the gate theory of pain, other stimuli can close gates in the spinal cord and block the transmission of pain. **206**
9. Placebos decrease pain, especially the emotional aspect of pain. Expecting pain can magnify the experience, a nocebo effect. **207**
10. The axons for itch transmit impulses more slowly than other sensations. They can be inhibited by pain messages. **207**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

capsaicin	**200**
dermatome	**201**
endorphins	**205**
gate theory	**206**

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neuropathic pain **206**
nocebo **207**
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Pacinian corpuscle **199**
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S1 **201**
semicircular canals **198**
somatosensory system **199**

Thought Question

How could you determine whether hypnosis releases endorphins?

Stop & Check Answers

11. The vestibular system enables the brain to shift eye movements to compensate for changes in head position. Without feedback about head position, a person would not be able to correct the eye movements, and the experience would be like watching a jiggling book page.

12. Jalapeños and other hot peppers contain capsaicin, which stimulates receptors that are sensitive to heat.

13. Conscious visual perception depends on V1 and conscious touch sensation depends on S1. Blindsight sometimes occurs after damage to V1, and numbsense sometimes occurs after damage to S1.

14. People are conscious of only those touch stimuli that produce sufficient arousal in S1. Also, activity in S1 responds to what someone experiences, even if it is an illusion.

15. The somatosensory cortex is necessary for perceiving the location and type of skin sensation. The insular cortex and anterior cingulate cortex respond to the pleasantness or unpleasantness.

16. You will lose pain sensation on the left side of the body because pain information crosses the spinal cord at once. You will lose touch sensation on the right side because touch pathways remain on the ipsilateral side until they reach the medulla.

17. Evidently the hypnotic suggestion decreased the response in the amygdala or areas associated with it, without decreasing activity in the somatosensory cortex.

18. Opiates block messages from the thinnest pain fibers, conveying dull pain, but not from thicker fibers, carrying sharp pain.

19. Damaged tissue releases chemicals that repair the damage but also magnify the responses of nearby pain receptors. Also, after tissue damage, axons conveying pain messages sprout to take over receptors previously sensitive to lighter touch.

20. The axons conveying pain rely mostly on sodium channel Nav1.7. People with a mutation in that channel report feeling no pain.

21. Placebos primarily relieve the emotional aspect of pain.

22. Opiates increase itch by blocking pain sensations. (Pain decreases itch.)

Module 6.2 | End-of-Module Quiz

1. The vestibular system is responsible for which of these behavioral observations?
- **a.** Foods have stronger taste while they are hot than while the same foods are cold.
- **b.** People can localize sounds well in the air, but poorly when they are underwater.
- **c.** People can describe the positions of their hands and feet without looking at them.
- **d.** People can read better while shaking their heads than while shaking the page.

2. Which of these experiences would cause greatest stimulation in the semicircular canals?
- **a.** Riding a roller coaster
- **b.** Lying in bed
- **c.** Waiting in line
- **d.** Drifting in a raft on a river

3. To what extent does the nervous system maintain separate representations of touch, heat, pain, and other aspects of somatic sensation?
- **a.** Not at all. A single type of receptor responds to all types of somatic sensation.
- **b.** The receptors vary, but all kinds of sensation merge in the spinal cord.
- **c.** The spinal cord has separate representations, but the various types merge in the cortex.
- **d.** Different types of sensation remain separate even in the cerebral cortex.

4. How do coldness receptors differ from heat receptors?
- **a.** Coldness receptors occur only in the hands and feet.
- **b.** Coldness receptors adapt quickly to an unchanging temperature.
- **c.** Coldness receptors also respond to chemicals, whereas heat receptors do not.
- **d.** Coldness receptors respond only to dangerous levels of cold.

5. How do the anterior cingulate cortex and related areas react to pain?
- **a.** They localize the painful spot on the body.
- **b.** They represent the emotional aspect.
- **c.** They close the pain gates in the spinal cord.
- **d.** They plan movements to reduce the source of pain.

6. Suppose your spinal cord is cut on the left side only. For the part of the body below that cut, you will lose pain sensation on the right side of the body and touch sensation on the left side. Why?
   - **a.** The left side of the body is more sensitive to pain than the right side is.
   - **b.** The right side of the body is more sensitive to pain than the left side is.
   - **c.** Pain axons cross the spinal cord at once, but touch fibers do not.
   - **d.** Pain axons regrow after injury, but touch axons do not.

7. What is "numbsense"?
   - **a.** The aftereffect of repeated, intense touch sensations
   - **b.** The ability to identify the location of a touch not felt consciously
   - **c.** The ability to imagine touch sensations
   - **d.** The sensations people report feeling in an amputated limb

8. Much of pain research has overlooked which of the following?
   - **a.** Differences between mild and intense pain
   - **b.** Differences between males and females
   - **c.** Differences between brief and prolonged pain
   - **d.** Differences between spinal mechanisms and brain mechanisms

9. What causes neuropathic pain?
   - **a.** Expectations of pain based on the setting or the instructions
   - **b.** Facilitation of pain receptors
   - **c.** Inhibition of Nav1.7 channels in axons
   - **d.** Gaps in the myelin covering axons

10. Which type of sensation reaches the brain by the slowest axons?
    - **a.** Discriminative touch
    - **b.** Vibration
    - **c.** Vestibular sensation
    - **d.** Itch

11. Which type of sensation inhibits itch sensations?
    - **a.** Olfaction
    - **b.** Taste
    - **c.** Pain
    - **d.** Hearing

Answers: 1d, 2a, 3d, 4b, 5b, 6c, 7b, 8b, 9b, 10d, 11c.

Module 6.3

The Chemical Senses

Learning Objectives

After studying this module, you should be able to:

- **8.** Describe the mechanisms of taste and smell.
- **9.** Discuss individual differences in taste and olfaction.
- **10.** Define and describe synesthesia.

Suppose you had the godlike power to create a new species of animal, but you could equip it with only one sensory system. Which sense would you give it?

Your first impulse might be to choose vision or hearing because of their importance to humans. But an animal with only one sensory system is not going to be much like humans, is it? And if it had only vision, and never tasted anything or felt pain or touch, would it have any idea what those visual stimuli meant? To have any chance of survival, your animal will have to be small and slow. What sense will be most useful to such an animal?

Theorists believe that the first sensory system of the earliest animals was a chemical sensitivity (G. H. Parker, 1922). A chemical sense enables a small animal to find food, avoid certain kinds of danger, and even locate mates.

Now imagine that you have to choose one of your senses to lose. Which one will it be? Most of us would not choose to lose vision, hearing, or touch. Losing pain sensitivity can be dangerous. You might choose to sacrifice your smell or taste.

Curious, isn't it? If an animal is going to survive with only one sense, it almost has to be a chemical sense, and yet to humans, the chemical senses seem dispensable. Perhaps we underestimate their importance.

Taste

Vision, hearing, and touch provide useful information for many purposes, but taste is useful only for telling us whether to swallow something or spit it out. That function is more important for some species than for others. Dolphins have almost no taste receptors (Jiang et al., 2012). Because they eat only fish, and swallow them whole, they have little need for the sense of taste. Cats, hyenas, seals, and sea lions have no sweetness receptors (Jiang et al., 2012). Being carnivores (meat eaters), they do not choose their food by sweetness. If you witness a cat lapping up milk, it is going for the proteins or fats, not the sweetness.

Taste results from stimulation of the **taste buds**, the receptors on the tongue. When we talk about the taste of food, we generally mean flavor, which combines taste and smell. Taste and smell axons converge onto many of the same cortical cells, enabling them to combine their influences (W. Fu et al., 2004).

Taste Receptors

The receptors for taste are not true neurons but modified skin cells. Like neurons, taste receptors have excitable membranes and release neurotransmitters to excite neighboring neurons, which in turn transmit information to the brain. Like skin cells, however, taste receptors are gradually sloughed off and replaced, each one lasting 10 to 14 days (Kinnamon, 1987).

Mammalian taste receptors are in taste buds located in **papillae** on the surface of the tongue (Figure 6.19). A given papilla may contain up to 10 or more taste buds (Arvidson and Friberg, 1980), and each taste bud contains about 50 receptor cells.

In adult humans, taste buds lie mainly along the edge of the tongue. You can demonstrate this principle as follows: Soak a small cotton swab in sugar water, salt water, or vinegar. Touch it lightly on the center of your tongue, not too far toward the back. If you get the position right, you will experience little or no taste. Then try it again on the edge of your tongue and notice the taste.

Try It Yourself

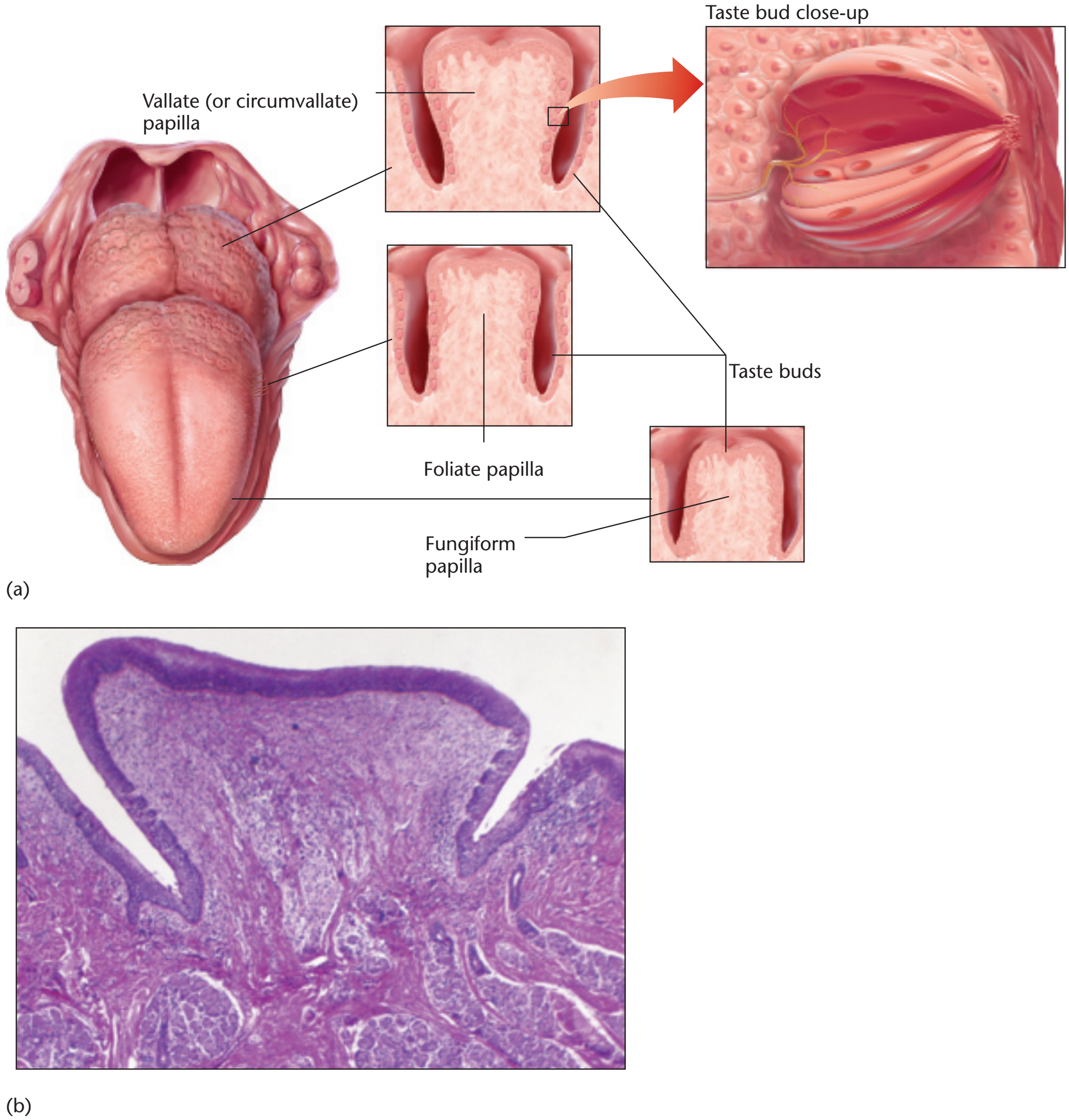
Now change the procedure a bit. Wash your mouth out and prepare a swab as before. Touch the soaked portion to one edge of your tongue and then slowly stroke it to the center of your tongue. It will seem as if you are moving the taste to the center of your tongue. In fact, you are getting only a touch sensation from the center of your tongue. You attribute the taste you had on the side of your tongue to any other spot you stroke (Bartoshuk, 1991).

How Many Kinds of Taste Receptors?

Traditionally, people in Western society have described tastes in terms of sweet, sour, salty, and bitter. However,

Figure 6.19 The organs of taste

(a) The tip, back, and sides of the tongue are covered with taste buds. Taste buds are located in papillae. (b) Photo showing cross-section of a taste bud. Each taste bud contains about 50 receptor cells.



(**Source:** ©Argosy Publishing Inc.; Biophoto Associates/Science Source.)

some tastes defy categorization in terms of these four labels (Schiffman and Erickson, 1980; Schiffman et al., 1980). How could we determine how many kinds of taste we have?

One way to identify taste receptor types is to find procedures that alter one receptor but not others. For example, chewing a miracle berry (native to West Africa) gives little taste itself but temporarily changes sweet receptors. Miracle berries contain a protein—miraculin—that modifies sweet receptors, enabling acids to stimulate them (Bartoshuk et al., 1974). If you try miracle berry extracts (available via the Internet), anything acidic will taste sweet in addition to its usual sour taste for the next half hour. Some people use these extracts as diet aids, so they can get sweet tastes without the calories.

But don't overdo it. A colleague and I once spent an evening experimenting with miracle berries. We drank straight lemon juice, sauerkraut juice, even vinegar. All tasted extremely sweet, but we awoke the next day with mouths full of ulcers. Those things are still acids, even when you make them taste sweet.

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Have you ever drunk orange juice just after brushing your teeth? How could something so wonderful suddenly taste so bad? Most toothpastes contain sodium lauryl sulfate, a chemical that intensifies bitter tastes while it coats the sweet receptors and prevents anything from reaching them (DeSimone et al., 1980; Schiffman, 1983).

Another taste-modifying substance is an extract from the plant *Gymnema sylvestre* (R. A. Frank et al., 1992). Some health food and herbal remedy stores sell dried leaves of *G. sylvestre*, from which you can brew a tea. (*G. sylvestre* pills won't work for this demonstration.) Soak your tongue in the tea for 30 seconds and then try tasting various substances. Salty, sour, and bitter substances taste the same as usual, but sugar becomes tasteless. Candies taste sour, bitter, or salty. (Those tastes were already present, but the sweetness overpowered them.) Curiously, the artificial sweetener aspartame (NutraSweet®) loses only some, not all, of its sweetness, implying that we have more than one type of sugar receptor (Schroeder and Flannery-Schroeder, 2005). This demonstration is probably risky for anyone with diabetes, because *G. sylvestre* also alters sugar absorption in the intestines. Also note: A side effect of this demonstration is greenish bowel movements for the next few days. Don't panic if you notice that little souvenir of your experience. The overall point of these demonstrations is that we do have receptors that are sensitive to one taste or another.

Try It Yourself

Further evidence for separate types of taste receptors comes from studies of the following type: Soak your tongue for 15 seconds in a sour solution, such as unsweetened lemon juice. Then try tasting some other sour solution, such as dilute vinegar. You will find that the second solution tastes less sour than usual, and perhaps not sour at all. This phenomenon, called **adaptation**, reflects the fatigue of receptors sensitive to sour tastes. Now try tasting something salty, sweet, or bitter. These substances taste about the same as usual. In short, you fail to exhibit **cross-adaptation**—reduced response to one taste after exposure to another (McBurney and Bartoshuk, 1973). You just demonstrated that the sour receptors differ from the other taste receptors. In similar ways you can demonstrate that salt receptors differ from the others and so forth.

Try It Yourself

Although we have long known that people have at least four kinds of taste receptors, several types of evidence suggest a fifth, glutamate, as in monosodium glutamate (MSG). The tongue has a glutamate receptor that resembles the neurotransmitter receptors for glutamate (Chaudhari et al., 2000). Glutamate tastes somewhat like unsalted chicken broth. The English language had no word for this taste, so it adopted the Japanese word *umami*. It is possible that we also have a taste receptor for fats, although that idea remains controversial (Roper and Chaudhari, 2017; Running et al., 2015).

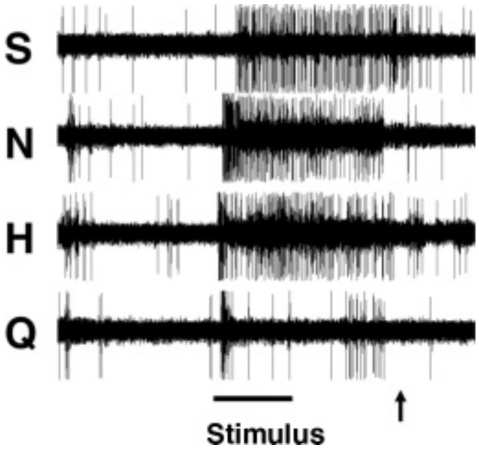
What about the taste of water? Water has a distinctive texture, but the experience of water is more than just the texture. Water replaces the bicarbonate ions usually present in the saliva on the tongue, and when it does so it changes the acid-to-base ratio and mildly stimulates the same receptors that detect sour tastes. Mice that lack sour receptors cannot distinguish between water and thin silicone oil, and they drink either one equally when thirsty (Zocchi et al., 2017).

In addition to the fact that different chemicals excite different receptors, they also produce different rhythms of action potentials. For other senses we assume, rightly or wrongly, that what matters is the number of action potentials per unit of time. In taste, the temporal pattern is also important, possibly more important. Figure 6.20 illustrates the responses of a brain neuron to five-second presentations of sucrose (sweet), NaCl (salty), HCl (sour), and quinine (bitter). This neuron responded to all four, but with different patterns over time (Di Lorenzo et al., 2009). Researchers stimulated rats' brain cells responsive to taste with an electrical pattern matching that for quinine. The rats backed away from whatever they were drinking at the time, reacting as if they were tasting something bitter (Di Lorenzo et al., 2009). Electrical stimulation at other temporal patterns did not cause this reaction.

Jalapeños and other hot peppers produce a hot mouth sensation that is not considered a taste. The evolution of hot peppers is an interesting story. The capsaicin in hot peppers discourages mammals but not birds, because birds'

Figure 6.20 Responses of a cell in a rat brain to four tastes

Each taste was presented for 5 seconds, marked by the Stimulus line at the bottom. Responses persisted until the tongue was washed with water, at the point marked by the arrow. The four lines represent S = sucrose (sweet), N = NaCl, table salt (salty), H = HCl, hydrochloric acid (sour), and Q = quinine (bitter).



(**Source:** From "Quality time: Representation of a multidimensional sensory domain through temporal coding," by P. M. Di Lorenzo, J.-Y. Chen, & J. D. Victor, 2009, Journal of Neuroscience, 29, pp. 9227–9238 Copyright © 2009 Used with permission of Society for Neuroscience permission conveyed through Copyright Clearance Center, Inc.)

heat receptor does not respond to capsaicin. A bird that eats a jalapeño eventually excretes the seeds, undigested, along with the other components of bird poop that serve as fertilizer. In the process, the bird spreads the seeds and nourishes their growth. Mammals, in contrast, chew any seeds that they eat, rendering them inactive. Jalapeños and similar plants gain an advantage by discouraging mammals but permitting birds to eat them.

Mechanisms of Taste Receptors

The saltiness receptor is simple. Recall that a neuron produces an action potential when sodium ions cross its membrane. A saltiness receptor simply permits sodium ions on the tongue to cross its membrane, and thereby detects the presence of sodium (DeSimone et al., 1984; Schiffman et al., 1983). Sour receptors detect the presence of acids (Huang et al., 2006).

Sweetness, bitterness, and umami receptors resemble metabotropic synapses. After a molecule binds to one of these receptors, it activates a G protein that releases a second messenger within the cell. People have two types of sweetness receptors and two types of umami receptors, each with somewhat different sensitivities (Barretto et al., 2015).

Bitter taste used to be a puzzle because bitter substances include a long list of dissimilar chemicals. Their only common factor is that they are to some degree toxic. What receptor could identify such a diverse set of chemicals? The answer is that we have not one bitter receptor but a family of approximately 30 that respond to different sets of compounds (Barretto et al., 2015; Born et al., 2013; Matsunami et al., 2000). Our large number of bitter receptors enable us to detect a great variety of dangerous chemicals.

Many bitter chemicals also trigger receptors in the nose, provoking coughing and sneezing if you happen to inhale them (Tizzano et al., 2010). Bitter chemicals are toxic, and the body does what it can to expel them.

Stop & Check

23. How do taste receptors differ from neurons?
24. What do we conclude if two tastes produce cross-adaptation?
25. What evidence implies that we detect tastes partly by the timing pattern of neuron responses?

See page 221 for the answer.

Taste Coding

Let's contrast two ways of coding sensory information. We sense pain by a *labeled line.* Anything that excites a pain axon reaches the brain as a pain sensation. In contrast, color vision requires an *across-fiber pattern,* or *combinatorial coding. A* certain level of response by a medium-wavelength cone in your retina might indicate dim light at 525 nm, brighter light at 475 nm, or still brighter light at 600 nm. The only way to resolve the ambiguity is to compare it with the responses of the other types of cones.

Which way do taste neurons use? Most taste receptors respond only to one type of chemical, but some respond to both sweet and salty, or sweet and umami. The receptors feed into neurons that might respond just to one taste, or to several (Wilson et al., 2022). By the time information reaches cells in the insula in the cortex (Figure 6.21), most cells respond most strongly to one taste, partly to others also, and in many cases also to odors, hunger, emotions, and other influences. The insula is not arranged in clusters of cells that respond mainly to one taste or another (Chen et al., 2021; Staszko et al., 2020). Because the response of any cortical taste cell is ambiguous, the meaning requires a comparison across cells (Erickson, 1982; Ohla et al., 2019).

Variations in Taste Sensitivity

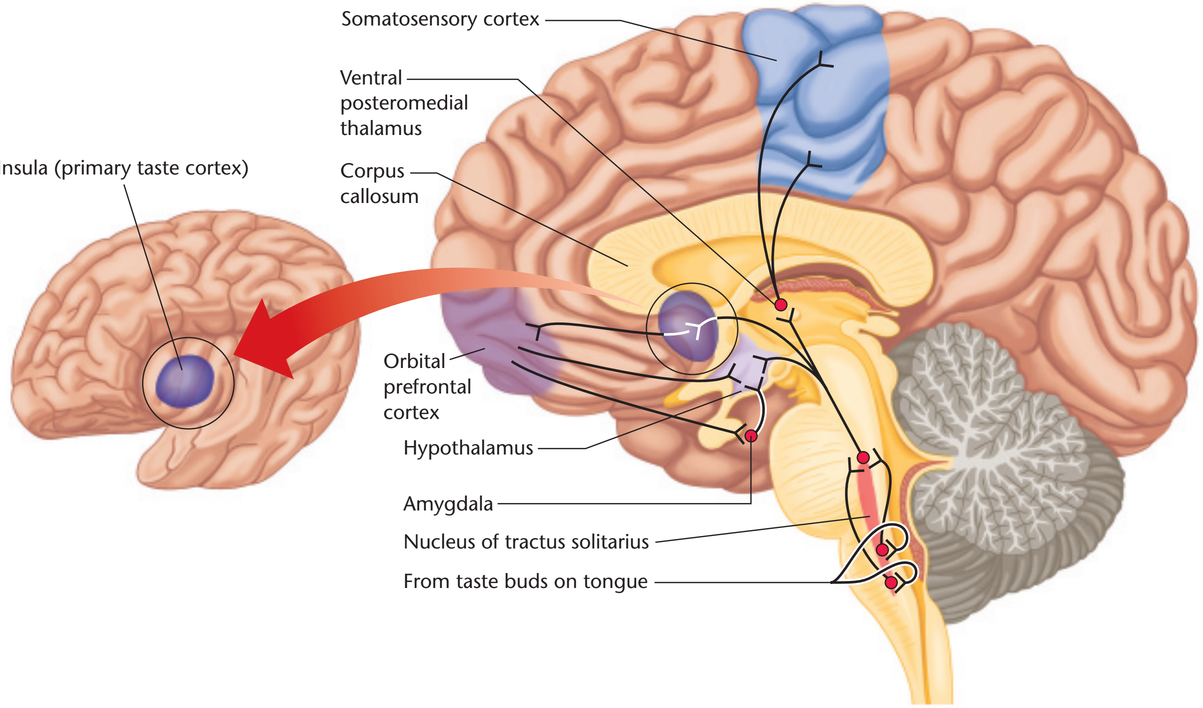
It is easy to assume that foods taste the same to everyone else as they do to you. And if we ask people to describe how strong various foods taste, they agree on which foods have bland, strong, or very strong flavors. However, when you say some food has a strong taste, you mean that it is strong compared to your other experiences. You do not know how they compare to someone else's. Some people have three times as many taste buds as other people do on the fungiform papillae near the tip of the tongue (Hayes et al., 2008) (Figure 6.22). Those with the greatest number are called **supertasters**, and those with average or below-average numbers are tasters or non-tasters (a misleading term). Several genes have significant effects (Dioszegi et al., 2019; Kim et al., 2003), but the variation also depends on age, hormones, and other influences. A person's taste sensitivity reaches its maximum during early pregnancy (Prutkin et al., 2000). That tendency is probably adaptive, because a pregnant person needs to be careful to avoid harmful foods.

People with the most taste buds tend to dislike strongly flavored foods, especially foods with a bitter taste. People with the fewest taste buds tolerate somewhat bitter tastes. However, these tendencies have many exceptions, because food preferences depend on familiarity and other influences.

Researchers have collected extensive data about the percentage of non-tasters in different populations, as demonstrated in Figure 6.23 (Guo and Reed, 2001). The figure depicts no obvious relationship between taste buds and cuisine. For example, non-tasters are common in India, where the food is spicy, and also in Britain, with relatively bland foods.

Figure 6.21 Major routes of impulses related to taste in the human brain

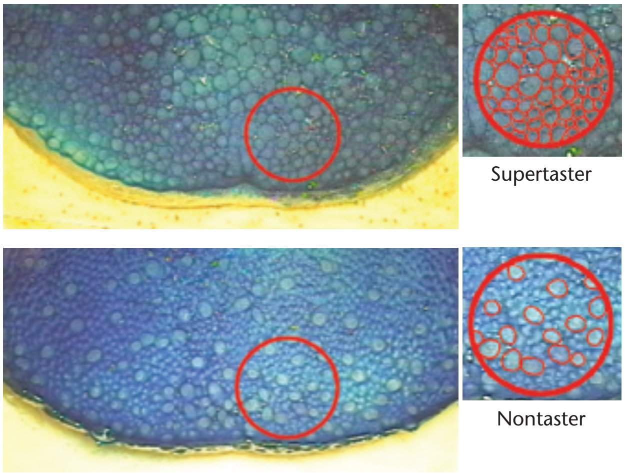
The thalamus and cerebral cortex receive impulses from both the left and the right sides of the tongue.


Somatosensory cortex
Ventral posteromedial thalamus
Insula (primary taste cortex)
Corpus callosum
Orbital prefrontal cortex
Hypothalamus
Amygdala
Nucleus of tractus solitarius
From taste buds on tongue

(**Source:** Based on Rolls, 1995)

Figure 6.22 Fungiform papillae on the human tongue

People with a greater density of papillae (top) are supertasters, with strong reactions to intense tastes. People with fewer papillae are tasters or non-tasters (bottom).


Supertaster

Nontaster

Linda Bartoshuk

If you would like to classify yourself as a taster, non-taster, or supertaster, follow the instructions in Table 6.2.

Try It Yourself

Table 6.2 | Are You a Supertaster, Taster, or Non-taster?

Equipment: ¼-inch hole punch, small piece of wax paper, cotton swab, blue food coloring, flashlight, and magnifying glass

Make a ¼-inch hole with a standard hole punch in a piece of wax paper. Dip the cotton swab in blue food coloring. Place the wax paper on the tip of your tongue, just right of the center. Rub the cotton swab over the hole in the wax paper to dye a small part of your tongue. With the flashlight and magnifying glass, have someone count the number of pink, unstained circles in the blue area. They are your fungiform papillae. Compare your results to the following averages:

Supertasters:	25 papillae
Tasters:	17 papillae
Non-tasters:	10 papillae

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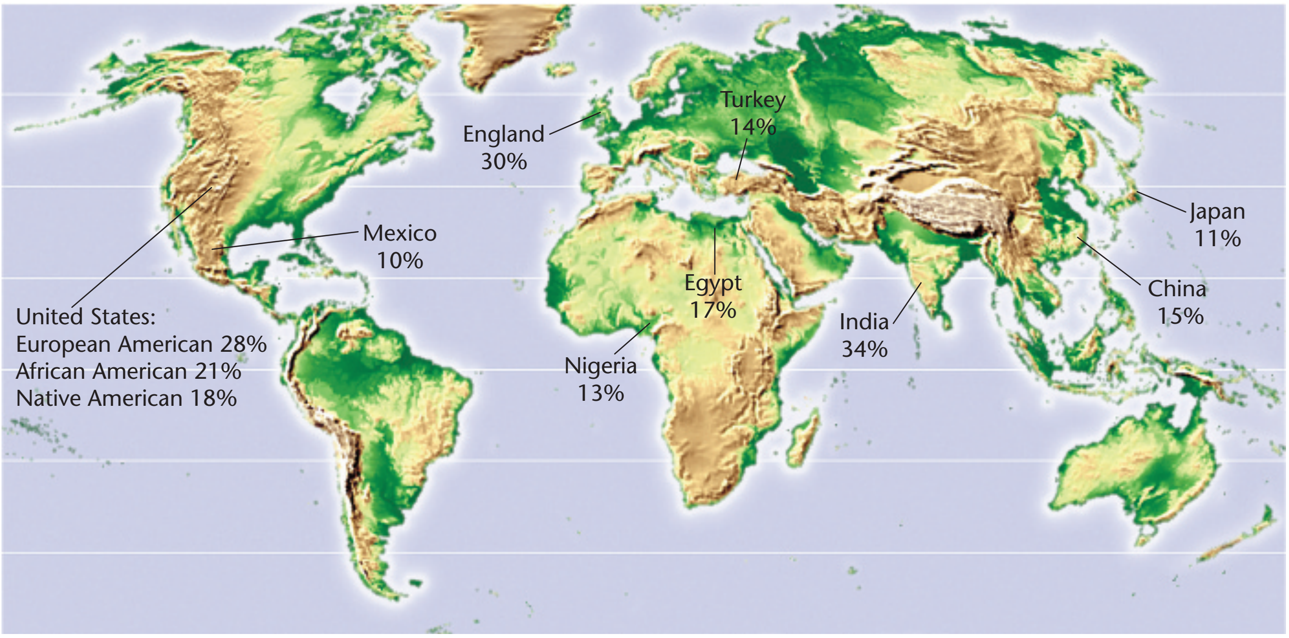
Figure 6.23 Percentage of non-tasters in several human populations

Most of the percentages are based on large samples, including more than 31,000 in Japan and 35,000 in India.



(**Source:** Based on Guo and Reed, 2001)

Stop & Check

26. Why are supertasters more sensitive to tastes than other people are?

See page 221 for the answer.

Olfaction

Olfaction, the sense of smell, is the response to chemicals that contact the membranes inside the nose. Olfaction is important for selecting and enjoying food. Try holding your nose while you eat, and notice how much flavor you lose. Olfaction is also useful for much else. Rats and mice exhibit an immediate, unlearned avoidance of the smells of cats, foxes, and other predators (Kondoh et al., 2016), unless they lack one particular olfactory receptor, in which case they approach without fear (Kobayakawa et al., 2007).

People are moderately accurate at smelling whether someone else is male or female, young or old, healthy or sick (de Groot et al., 2017), and also at smelling whether someone is afraid (de Groot et al., 2021). The smell of a sweaty female increases a male's testosterone secretions, especially if the female is near her time of ovulation. This effect is stronger for heterosexual males than for homosexual males (Miller and Maner, 2010; Savic et al., 2005). The smell of a sweaty male does not increase sexual arousal in females. Instead, it increases release of cortisol, a stress hormone (Wyart et al., 2007). Evidently a male reacts to a sweaty female as sexy, and a female reacts to a sweaty male as dangerous (Figure 6.24).

Consider the star-nosed mole and water shrew, two species that forage along the bottom of ponds and streams for worms, shellfish, and other invertebrates. We might assume that olfaction would be useless underwater, but these animals exhale tiny air bubbles onto the ground and then

Gary Meszaros/Science Source

This star-nosed mole is one of several species that uses their olfactory sense underwater.

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Figure 6.24 Male sweat elicits a stress hormone

Research has found that females respond to the smell of a sweaty male by releasing cortisol, a stress hormone.

NamtipStudio/Shutterstock.com

inhale them again. By doing so, they can follow an underwater trail well enough to track their prey (Catania, 2006).

We marvel at feats like this and at the ability of a bloodhound to find someone by following an olfactory trail through a forest, and we assume that we could never do anything like that. One big reason is that we stand upright, with our noses far above the ground! What if you got down on your hands and knees and put your nose to the ground? Researchers blindfolded 32 young adults, made them wear gloves, and then asked them to try to follow a trail of chocolate scent across a field. Most of the participants succeeded (slowly), and they improved their performance with practice. Humans detect odors better than we generally imagine (McGann, 2017), although most of us are poor at naming the odors we detect (Young, 2020). Check the YouTube video "People following a scent trail."

Olfactory Receptors

The neurons responsible for smell are the **olfactory cells** that line the olfactory epithelium in the rear of the nasal air passages Figure 6.25). In mammals, receptors are on the olfactory cell's cilia (threadlike dendrites) that extend into the mucous surface of the nasal passage. They detect both the chemicals of the air you inhale (*orthonasal* olfaction) and the chemicals given off by food in your mouth (*retronasal* olfaction).

How many kinds of olfactory receptors do we have? For many years, researchers expected to find a few "primary" odors, just as people can combine three primary colors to match all the others. A popular guess was that we might have seven primary odors. Then, after years of persistent and discouraging efforts, Linda Buck and Richard Axel (1991) identified a family of proteins in olfactory receptors, as displayed in Figure 6.26. But the number was not seven. Humans have several hundred types of olfactory receptors, while rats and mice have about a thousand and elephants have about two thousand (Kurian et al., 2021; X. Zhang and Firestein, 2002). Ocean-dwelling mammals have far fewer (Liu et al., 2019). Why did evolution have to design so many olfactory receptor types? Color vision gets by with just three. The reason is that light energy can be arranged along a single dimension, wavelength. The chemicals that we smell do not range along a single continuum.

Like metabotropic neurotransmitter receptors, each olfactory receptor protein traverses the cell membrane seven times and responds to a chemical outside the cell (an odorant molecule) by triggering changes in a G protein inside the cell. The G protein evokes chemical activities that lead to an action potential.

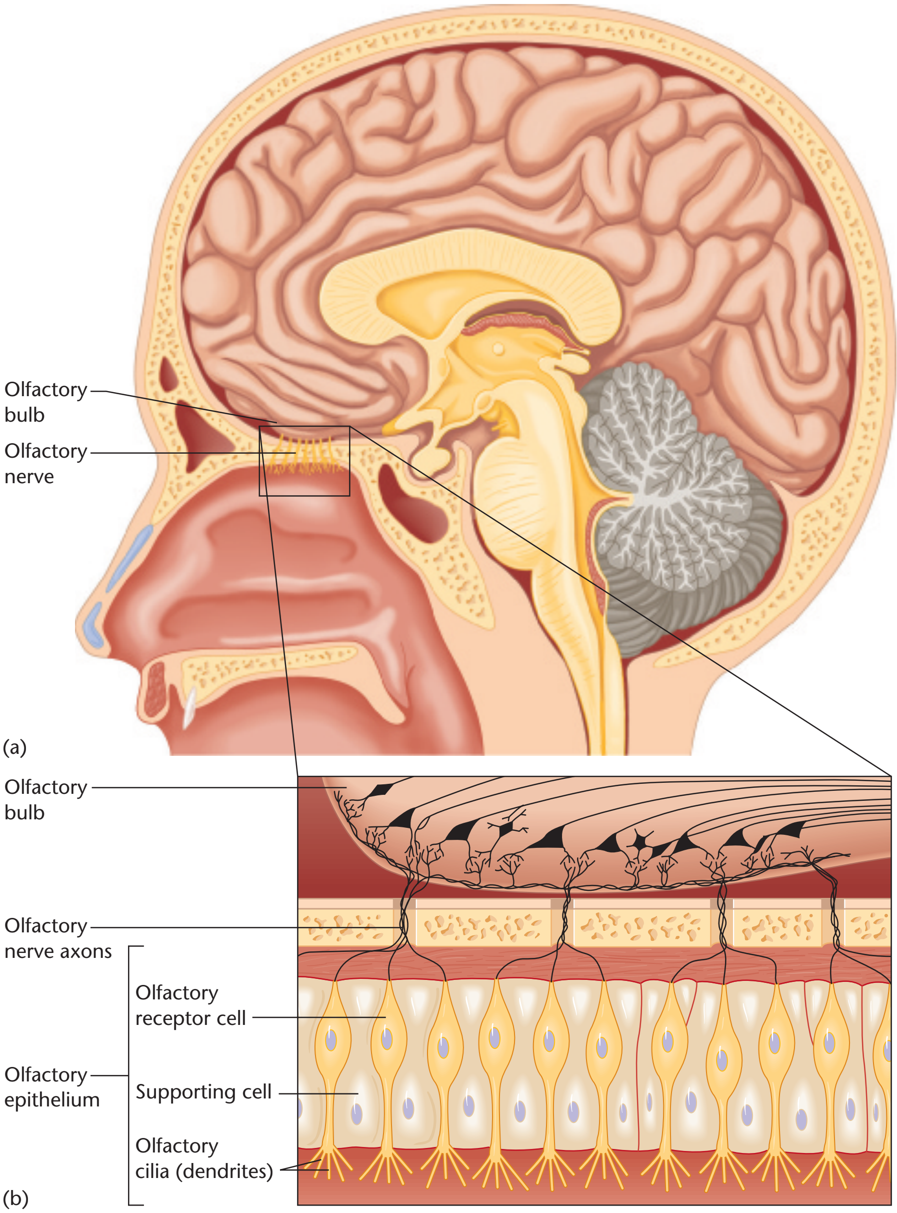
Olfactory receptors are vulnerable to damage because they are exposed to the air. Unlike your receptors for vision and hearing, which remain with you for a lifetime, an olfactory receptor has an average survival time of just over a month. At that point, a stem cell matures into a new olfactory cell in the same location as the first and expresses the same receptor protein (Nef, 1998). Its axon then finds its way to the correct target in the olfactory bulb. Each olfactory neuron axon contains copies of its olfactory receptor protein, which it uses like an identification card to find its correct partner (Barnea et al., 2004; Strotmann et al., 2004). However, if the entire olfactory surface is damaged at once by a blast of toxic fumes so that the system has to replace all

Linda Buck (b. 1947)

How could humans and other mammals detect 10,000 or more odorous chemicals, and how could nearly identical chemicals generate different odor perceptions? … It was obvious to me that the first step … meant finding odorant receptors, a class of molecules that had been proposed to exist, but had not been found. I decided that this is what I had to do…. Looking at the first sequences of odorant receptors obtained from rat, I was moved by Nature's marvelous invention. This work showed that the rat has a multigene family that codes for in excess of one hundred different odorant receptors, all related, but each one unique. (Buck, 2004)

Figure 6.25 Olfactory receptors

(a) Location of receptors in nasal cavity. (b) Close-up of olfactory cells.


Olfactory bulb
Olfactory nerve
(a)
Olfactory bulb
Olfactory nerve axons
Olfactory receptor cell
Olfactory epithelium
Supporting cell
Olfactory cilia (dendrites)
(b)

the receptors at the same time, many of them fail to make the correct connections, and olfactory experience does not fully recover (Iwema et al., 2004).

Stop & Check

27. How do olfactory receptors resemble metabotropic neurotransmitter receptors?

See page 221 for the answer.

Olfactory Coding

The diversity of olfactory receptors makes possible narrow specialization of functions. Each olfactory cell has only one receptor type, and most receptors respond to either just one chemical or several closely related chemicals. A few receptors are more broadly tuned. Some receptors respond synergistically; that is, they respond to a combination of two chemicals, but hardly at all to either one alone (Hanchate et al., 2015; Kurian et al., 2021).

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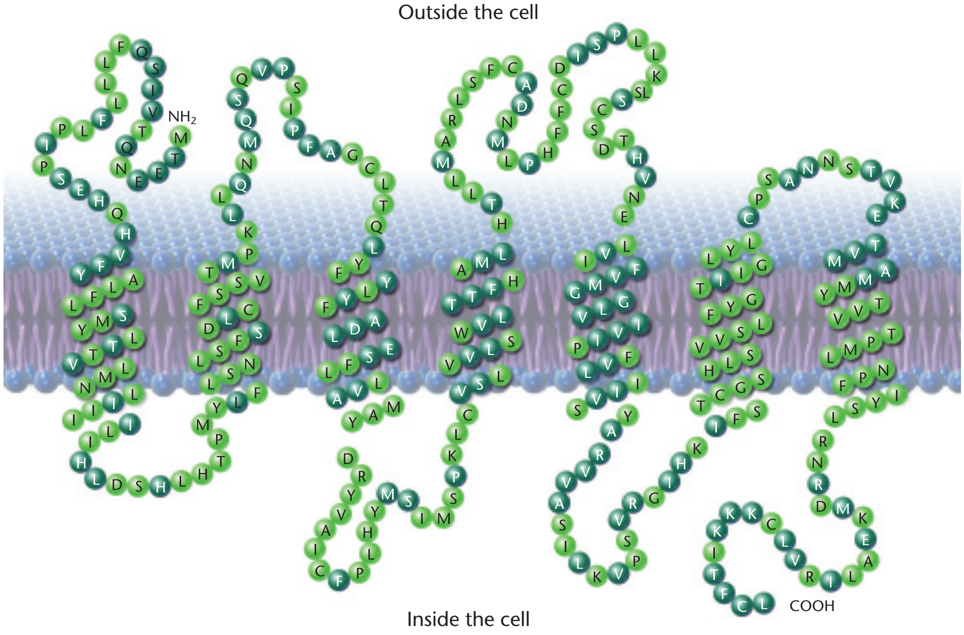
Figure 6.26 An olfactory receptor protein

Like a synaptic receptor protein, this olfactory receptor responds to a chemical outside the cell and triggers activity of a G protein inside the cell. Olfactory receptors differ slightly in their structure. Each little circle in this diagram represents one amino acid of the protein. The lighter circles represent amino acids that are the same in most olfactory receptor proteins, and the darker ones represent more variable ones.



(**Source:** Based on Buck and Axel, 1991)

Although the receptors are arranged haphazardly along the nasal cavity, all the receptors sensitive to a particular chemical or combination of chemicals connect to a single cluster in the olfactory bulb, called a *glomerulus* (Figures 3.12 and 6.25) (Horowitz et al., 2014; Lodovici, 2021). The arrangement of glomeruli does not form an obvious pattern. That is, nearby glomeruli do not necessarily respond to similar odors (Chae et al., 2019).

When we get to the primary olfactory cortex, known as the *piriform cortex*, things are different. The glomeruli send their axons diffusely, almost haphazardly, to the piriform cortex. Whereas each glomerulus responds to just one chemical, each cell in the piriform cortex responds to a combination of chemicals, such as the smell of berries or melons (Yoshida and Mori, 2007). Because each neuron responds to a combination of influences, its response does not identify a single odorant. Furthermore, the response of any cell in the piriform cortex changes over time. The odors that stimulate it today may not be the same ones that will stimulate it next week. The piriform cortex has been compared to a "scratch pad" that stores temporary memories (Schonover et al., 2021). How the cortex recognizes an odor remains a puzzle.

Individual Differences

People vary in their sense of smell more than you might guess. Most of the genes controlling olfactory receptors have variant forms, and on average, two people chosen at random probably differ in about 30 percent of their olfactory receptor genes (Mainland et al., 2014). Compared to anyone else you know, you probably experience some smells as stronger, some as weaker.

In addition to differences based on genes, odor sensitivity declines with age. The decline varies among odors. Sensitivity to mushroom odor remains nearly constant as people age, sensitivity to onion odor declines moderately, and sensitivity to rose odor declines greatly (Seow et al., 2016). A sharp decline in odor sensitivity is often an early symptom of Alzheimer's disease or Parkinson's disease (Doty and Kamath, 2014).

Many people who were infected by the worldwide pandemic of COVID-19 suffered an impaired sense of smell, with slow recovery over weeks. The virus probably does not enter human neurons, but it damages the skin cells that support the olfactory receptors in the nose (Brann et al., 2020).

Humane females detect odors more readily than males, at all ages and in all cultures that researchers have tested

(Doty et al., 1985; Saxton et al., 2014; Yousem et al., 1999). In addition, if people repeatedly attend to a faint odor, young adult females become more and more sensitive to it, until they can detect it in concentrations one ten-thousandth of what they could at the start (Dalton et al., 2002). Males, prepubescent females, and post-menopausal females do not demonstrate that effect, so it apparently depends on female hormones. We can only speculate on why we evolved a connection between female hormones and odor sensitization.

Stop & Check

28. How do neurons in the olfactory cortex differ from neurons in the olfactory bulb?
29. What factors contribute to individual differences in olfactory sensitivity?

See page 222 for the answer.

Synesthesia

Finally, let's consider something that is not one sense but a combination: **Synesthesia** is the experience some people have in which stimulation of one sense evokes a perception of that sense and another one also. For example, someone might perceive the letter J as green or say that each taste feels like a particular shape on the tongue (Barnett et al., 2008). In the words of one person, "To me, the taste of beef is dark blue. The smell of almonds is pale orange. And when tenor saxophones play, the music looks like a floating, suspended coiling snake-ball of lit-up purple neon tubes" (Day, 2005, p. 11).

Various studies attest to the reality of synesthesia. People reporting synesthesia have increased amounts of gray matter in certain brain areas and altered connections to other areas (Jäncke et al., 2009; Rouw and Scholte, 2007; Weiss and Fink, 2009). People who perceive colors in letters and numbers have increased connections between the brain areas responding to colors and those responding to letters and numbers (Tomson et al., 2013). They also exhibit behavioral characteristics that would be hard to pretend. Try to find the 2 among the 5s in each of the following displays:

555555555555	**555555555555**	**555555555555**
555555555555	**555555555555**	**552555555555**
555555525555	**555555555555**	**555555555555**
555555555555	**555555555525**	**555555555555**

One man with synesthesia could find the 2 consistently faster than other people, explaining that he just looked for a patch of orange! However, he was slower than other people to find an 8 among 6s because both 8 and 6 look blue to him (Blake et al., 2005). Another person had trouble finding an A among 4s because both look red but could easily find an A among 0s because 0 looks black (Laeng et al., 2004). Oddly, however, someone who sees the letter P as yellow had no trouble finding it when it was printed in black ink on a yellow page. In some way, he sees the letter both in its real color (black) *and* its synesthetic color (Blake et al., 2005).

What causes synesthesia? In some cases it reflects a genetic predisposition (Tilot et al., 2018), and it frequently occurs in the same families as people with absolute pitch, suggesting a genetic link between the conditions (Gregerson et al., 2013). However, obviously people are not born with a letter-to-color or number-to-color synesthesia. In some cases, we know where people learned their associations. Researchers found 10 people with synesthesia whose associations matched or nearly matched the colors of Fisher-Price refrigerator magnets they had used as children, such as red A, yellow C, and green D (Witthoft and Winawer, 2013). Only a small percentage of children who play with these magnets develop synesthesia, and most people with synesthesia have other associations, so the toys represent only one part of the explanation.

When people misperceive a stimulus—as in an illusion—their synesthetic experience corresponds to what the person *thought* the stimulus was, not what it actually was (Bargary et al., 2009). This result implies that the phenomenon occurs in the cerebral cortex, not in the receptors or their first connections to the nervous system. Furthermore, for some people, the idea of a word triggers a synesthetic experience before they have thought of the word itself. One person who could not think of "castanets" said it was on the tip of the tongue . . . not sure what the word was, but it tasted like tuna (Simner and Ward, 2006). A man with color vision deficiency reported synesthetic colors that he does not see in real life. He calls them "Martian colors" (Ramachandran, 2003). Evidently, his brain can see all the colors, even though his cones cannot send the messages.

A popular hypothesis is that axons from one cortical area branch into another cortical area. This explanation does apply to at least some cases. One woman suffered damage to the somatosensory area of her right thalamus. Initially she was, as expected, insensitive to touch in her left arm and hand. Over a year and a half, she gradually recovered part of her touch sensation. However, during that period, the somatosensory area of her right cortex was receiving little input. Some axons from her auditory system invaded the somatosensory cortex. As a result, she developed an unusual auditory-to-touch synesthesia. Many sounds cause her to feel an intense tingling sensation in her left arm and hand (Beauchamp and Ro, 2008; Naumer and van den Bosch, 2009).

Stop & Check

30. What evidence indicates that people learn their synesthetic associations, at least in some cases?
31. If someone reports seeing a particular letter in color, in what way is it different from a real color?

See page 222 for the answer.

Module 6.3 | In Closing

Senses as Ways of Knowing the World

Ask someone to describe the current environment, and you will probably get a description of sights and sounds. If nonhumans could talk, most species would start by describing what they smell. A human, a dog, a bat, and a snail may be in the same place, but the environments they perceive are very different.

We sometimes underestimate the importance of taste and smell. People who lose their sense of taste say they no longer enjoy eating and find it difficult to swallow (Cowart, 2005). Many people who lose the sense of smell feel permanently depressed. Taste and smell cannot compete with vision and hearing for telling us about what is happening in the distance, but they are essential for the enjoyment of life.

Summary

1. Taste receptors are modified skin cells inside taste buds in papillae on the tongue. **211**
2. We have receptors sensitive to the tastes of sweet, sour, salty, bitter, umami (glutamate), and possibly fat. Taste is coded by the relative activity of different kinds of cells but also by the rhythm of responses within a given cell. **211**
3. Salty receptors respond simply to sodium ions crossing the membrane. Sour receptors respond to acids. Sweet, bitter, and umami receptors act by a second messenger within the cell, similar to the way a metabotropic neurotransmitter receptor operates. **214**
4. Mammals have 30 or more kinds of bitter receptors, enabling them to detect many types of harmful substances. **214**
5. People vary in their sensitivity to tastes, especially bitter tastes, because of variations in their number of taste buds. **214**
6. Olfactory receptors are proteins, each of them highly responsive to a few related chemicals and unresponsive to others. Vertebrates have hundreds of olfactory receptors, each sensitive to a few related chemicals. **217**
7. Olfactory neurons survive only a month or so. The new cells that replace them become sensitive to the same chemicals as the ones they replace, and they send their axons to the same targets. **217**
8. Olfactory neurons in the cerebral cortex respond to complex patterns, such as those of a food. **219**
9. People vary in their sensitivity to odors, because of differences in genetics, age, illness, and gender. **219**
10. Some people experience synesthesia, a sensation in one modality after stimulation in another one. For example, someone might visualize purple neon tubes while listening to saxophones. In some cases, the explanation is that axons from one sense have invaded brain areas responsible for a different sense. **220**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

adaptation	**213**
cross-adaptation	**213**
olfaction	**216**
olfactory cells	**217**
papillae	**211**
supertasters	**214**
synesthesia	**220**
taste bud	**211**

Thought Question

Suppose a chemist synthesizes a new chemical that turns out to have an odor. Presumably, we do not have a specialized receptor for that chemical. Explain how our receptors detect it.

Stop & Check Answers

23. Because taste receptors are modified skin cells, they are replaced about every two weeks.
24. If they produce cross adaptation, they must stimulate the same taste receptors.
25. When researchers stimulated rats brain cells with the same time pattern that quinine produces, the rats retreated and stopped drinking.
26. They have more taste buds near the tip of the tongue.
27. Like metabotropic neurotransmitter receptors, an olfactory receptor acts through a G protein that triggers further events within the cell.

28. Most neurons in the olfactory bulb respond only to one chemical or a few closely related chemicals. Neurons in the olfactory cortex respond to a combination of chemicals, as would be characteristic of a food, plant, or other object.

29. People differ in olfactory sensitivity because of genetics, age, illness, and gender.

30. Some people have letter-color synesthesias that match the colors of refrigerator magnets they played with in childhood.

31. Someone who perceives a letter as yellow (when it is actually in black ink) can nevertheless see it on a yellow page.

Module 6.3 | End-of-Module Quiz

1. What type of cell is a taste receptor?

- **a.** A neuron
- **b.** A modified skin cell
- **c.** A modified gland cell
- **d.** A modified muscle cell

2. The effects of miracle berries and *Gymnema sylvestre* support which of these conclusions?

- **a.** People from different cultures tend to have different taste preferences.
- **b.** Some of our receptors respond to a single taste.
- **c.** Increasing the temperature of a food enhances its flavors.
- **d.** Coding in the olfactory bulb differs from that in the olfactory cortex.

3. How do we detect the taste of water?

- **a.** By its texture alone
- **b.** By its effect on sour receptors
- **c.** By its effect on sweet receptors
- **d.** By a separate type of receptor

4. In addition to stimulating different receptors, how else do tastes vary?

- **a.** They stimulate either heat or cold receptors.
- **b.** They send axons to different lobes of the cortex.
- **c.** They produce different rhythms of neural activity.
- **d.** They stimulate different parts of the tongue.

5. The receptors for sweet, bitter, and umami tastes all resemble which of these?

- **a.** Metabotropic synaptic receptors
- **b.** The rods in the retina
- **c.** The hair cells of the auditory system
- **d.** Pain receptors

6. Why can we taste such a wide variety of chemicals as bitter?

- **a.** All bitter substances are chemically similar.
- **b.** We have 30 or more types of bitter receptors.
- **c.** We have a bitter receptor that is versatile enough to detect many types of chemicals.
- **d.** Sweet and sour receptors can detect bitter substances.

7. Why are some people more sensitive than others are to low concentrations of taste or smell?

- **a.** People with more activity in their prefrontal cortex pay more attention to sensations.
- **b.** People who know more words for taste or smell can remember and report them better.
- **c.** Some people have faster axons between the tongue and the brain.
- **d.** Some people have more taste receptors or odor receptors than others do.

8. Humans have how many types of olfactory receptors?

- **a.** Hundreds
- **b.** Seven
- **c.** Three
- **d.** Just one

9. Why do many people infected with COVID-19 have an impaired sense of smell?

- **a.** The virus damages olfactory receptors.
- **b.** The virus damages skin cells that support olfactory receptors.
- **c.** The virus damages connections from the olfactory bulb to the olfactory cortex.
- **d.** The virus itself stimulates olfactory receptors.

10. What behavioral evidence indicates that synesthesia is real, and not something that people claim to experience?

- **a.** Some people's associations match the colors of refrigerator magnets they played with in childhood.
- **b.** Many people change their synesthetic associations from one year to the next.
- **c.** People with synesthesia find a 2 among 5s faster than usual if they have different synesthetic colors, and slower if they have the same color.
- **d.** It is easy to teach someone to develop a synesthesia.

Answers: 1b, 2b, 3b, 4c, 5a, 6b, 7d, 8a, 9b, 10c.

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Suggestions for Further Reading

Barwich, A.S. (2020). *Smellosophy*. (Harvard University Press). Thorough description of research on the sense of smell and how it compares to other senses.

Henshaw, J. M. (2012). *A tour of the senses.* (Johns Hopkins University Press). Excellent explanation of the physics of hearing and other senses.

Horowitz, S. S. (2012). *The universal sense: How hearing shapes the mind.* (Bloomsbury). Entertaining description of sound, music, and the role of hearing in the lives of humans and other species.

Thernstrom, M. (2010). *The pain chronicles.* (Farrar, Straus and Giroux). Why can some people withstand terrible injuries with little apparent pain? Why do others suffer endlessly? This book explores these and other questions about pain.

Chapter 7

Ultimately, what brain activity accomplishes is the control of movement—a far more complex process than it might seem.
(Stanislaw Pytel/Stone/Getty Images)

Movement

Chapter Outline

Module 7.1
The Control of Movement
Muscles and Movements
Units of Movement
In Closing: Categories of Movement

Module 7.2
Brain Mechanisms of Movement
The Cerebral Cortex
The Cerebellum
The Basal Ganglia
Conscious Decisions and Movement
In Closing: Movement Control and Cognition

Module 7.3
Movement Disorders
Parkinson's Disease
Huntington's Disease
In Closing: Movement Disorders Affect More than Movement

Learning Objectives

After studying this chapter, you should be able to:

1. Distinguish between the functions of fast and slow muscles.
2. Describe the functions of proprioceptors.
3. Discuss the concept of a motor program.
4. Contrast the roles of several cortical areas in the control of movement.
5. Discuss the role of the prefrontal cortex in inhibiting movements.
6. Evaluate the concept of mirror neurons.
7. Contrast the anatomy and functions of the lateral and medial corticospinal tracts.
8. Describe the functions of the cerebellum and basal ganglia.
9. Evaluate the evidence regarding the role of consciousness in planning a movement.
10. Discuss the causes and treatment of Parkinson's disease.
11. Describe the genetics of Huntington's disease.

Try It Yourself

Before we get started, consider trying this: Take a pencil and a sheet of paper, and put the pencil in your nondominant hand. For example, if you are right-handed, put it in your left hand. Now, with that hand, draw a face in profile—that is, facing one direction or the other but not straight ahead. *If you are able, do this now before reading further.*

If you tried the demonstration, you probably notice that your drawing is more childlike than usual, as if part of your brain stored the way you used to draw as a young child. Now, for those who are right-handed, why did you draw it facing to the right? At least I assume you did, because more than two-thirds of right-handers drawing with their left hand draw the profile facing right. They revert to the pattern exhibited by young children. Up to about age 5 or 6, children drawing with the left hand almost always draw people and animals facing right, and when using the right hand, they almost always draw them facing left. But *why*? They say, "it's easier that way," but *why* is it easier that way? We have much to learn about the control of movement and how it relates to perception, motivation, and other functions.

Module 7.1

The Control of Movement

Learning Objectives

After studying this module, you should be able to:

1. Distinguish between the functions of fast and slow muscles.
2. Describe the functions of proprioceptors.
3. Discuss the concept of a motor program.

Why do we have brains? Plants survive just fine without one. So do sponges, which are animals, even if they don't act like them. But plants don't move, and neither do sponges. A sea squirt (a marine invertebrate) has a brain during its infant stage, when it swims, but when it transforms into an adult, it attaches to a surface, becomes a stationary filter feeder, and digests its own brain, as if to say, "Now that I've stopped traveling, I won't need this brain thing anymore." Ultimately, the purpose of a brain is to control behaviors, and behaviors are movements.

"But wait," you might reply. "We need a brain for other things, too, don't we? Like seeing, hearing, understanding speech . . ."

Well, what would be the value of seeing and hearing if you couldn't do anything? Understanding speech wouldn't do you much good unless you could do something about it. A brain without muscles would be like a computer without a monitor, printer, or other output. No matter how powerful the internal processing, it would be useless.

Reinhard Dirscherl/Alamy Stock Photo

Adult sea squirts attach to a surface, never move again, and digest their own brains.

Muscles and Movements

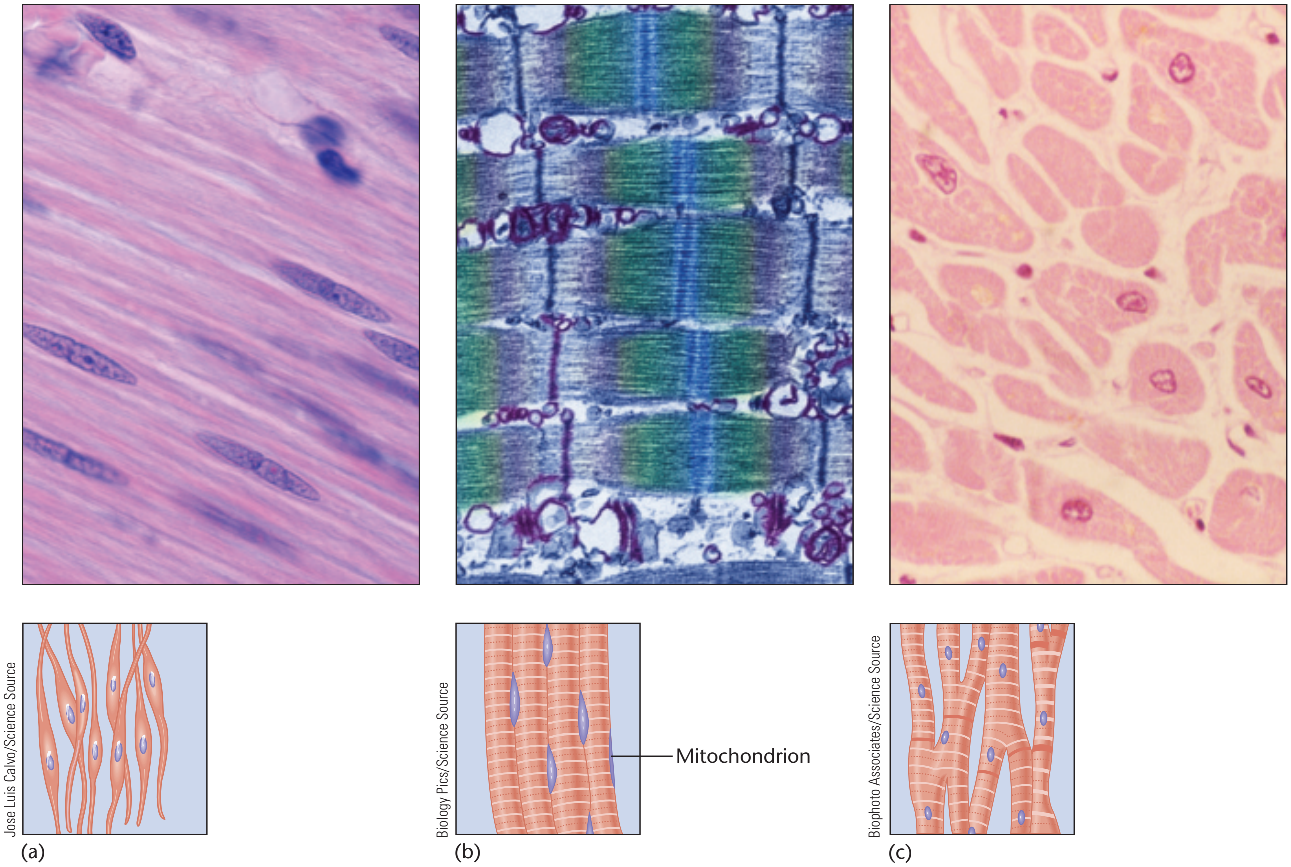
Movement depends on muscle contractions. Vertebrate muscles fall into three categories (Figure 7.1). **Smooth muscles** control the digestive system and other organs, **skeletal** or **striated muscles** control movement of the body in relation to the environment, and **cardiac muscles** control the heart.

Each muscle has many fibers, as Figure 7.2 illustrates. Although each muscle fiber receives information from only one axon, a given axon may innervate more than one muscle fiber. The eye muscles have a ratio of about one axon per three muscle fibers, and the biceps muscles of the arm have a ratio of one axon to more than a hundred fibers (Evarts, 1979). The difference allows the eye to move more precisely than the biceps.

A **neuromuscular junction** is a synapse between a motor neuron axon and a muscle fiber. An axon at a skeletal muscle releases acetylcholine at the neuromuscular junction, causing a muscle contraction. A deficit of acetylcholine or its receptors impairs movement. Each muscle makes just one movement, a contraction. There is no message to cause relaxation or to move a muscle in the opposite direction. Moving a leg or arm back and forth requires opposing sets of muscles, called **antagonistic muscles**. At your elbow, for example, your **flexor** muscle brings your hand toward your shoulder and your **extensor** muscle straightens the arm (Figure 7.3).

Figure 7.1 Vertebrate muscles

(a) Smooth muscle, found in the intestines and other organs, consists of long, thin cells. **(b)** Skeletal, or striated, muscle consists of long cylindrical fibers with stripes. **(c)** Cardiac muscle, found in the heart, consists of fibers that fuse together at various points. Because of these fusions, cardiac muscles contract together, not independently.



Jose Luis Calvo/Science Source

Biology Pics/Science Source

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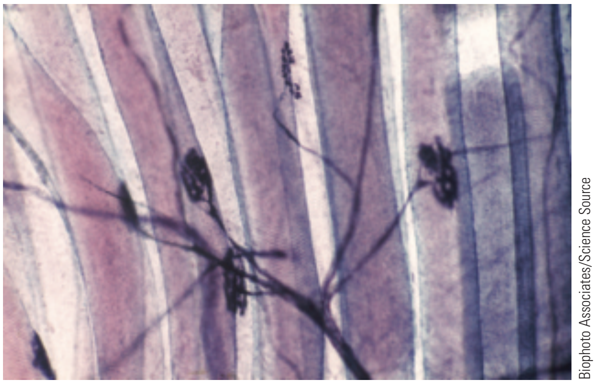
(**Source:** Illustrations after Starr and Taggart, 1989) All © Ed Reschke

Figure 7.2 An axon branching to innervate several muscle fibers

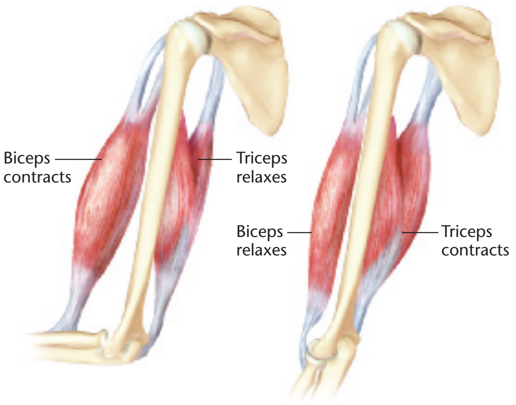
Movements can be more precise where each axon innervates only a few fibers, as with eye muscles, than where it innervates many fibers, as with biceps muscles.



Biophoto Associates/Science Source

Figure 7.3 Antagonistic muscles

The biceps of the arm is a flexor. The triceps is an extensor.



(**Source:** Starr & Taggart, 1989)

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Stop & Check

1. Why can we move the eye muscles with greater precision than the biceps muscles?
2. Is it possible to inhibit a skeletal muscle?

See page 232 for the answer.

Fast and Slow Muscles

Imagine you are a small fish. Your only defense against predators is your ability to swim away (Figure 7.4). Your temperature is the same as the water around you, and because muscle contractions are chemical processes, they slow down in the cold. When the water gets cold, presumably you move more slowly, right? Strangely, you do not. You have to use more muscles, but you swim at about the same speed (Rome et al., 1984).

Figure 7.4 Temperature and movement

Fish have the same temperature as the water around them, but many of their predators, such as this pelican, do not. At cold temperatures, each fish muscle contracts more slowly than usual, but a fish compensates by using more muscles.

Zimmytws/Shutterstock.com

A fish has three kinds of muscles: red, pink, and white. Red muscles produce the slowest movements, but they do not fatigue. White muscles produce the fastest movements, but they fatigue rapidly. Pink muscles are intermediate in both speed and rate of fatigue. In warm water, a fish uses mostly its red and pink muscles. In colder water, the fish uses more white muscles, maintaining its speed but fatiguing faster.

All right, you can stop imagining you are a fish. Human and other mammals have various kinds of muscle fibers mixed together, not in separate bundles as in fish. Our muscles range from **fast-twitch fibers** with fast contractions and rapid fatigue to **slow-twitch fibers** with less vigorous contractions and no fatigue (Hennig and Lømo, 1985). We rely on our slow-twitch and intermediate fibers, like a fish's red muscles, for the least strenuous activities, such as walking leisurely or talking. If you run up a steep hill at full speed, you switch to fast-twitch fibers that fatigue rapidly.

Slow-twitch fibers do not fatigue because they are **aerobic**—they use oxygen during their movements. You can think of them as "pay as you go." Fast-twitch fibers are **anaerobic**, using reactions that burn fatty acids without needing oxygen at the time, but requiring oxygen for recovery. Using fast-twitch fibers builds up an *oxygen debt.* If you are bicycling rapidly, at first your activity is aerobic, using slow-twitch fibers that use glucose and oxygen, but after a while your glucose supplies dwindle. Low glucose activates a gene that stops the muscles from using glucose, switching you to the fast-twitch muscles that depend on anaerobic use of fatty acids (Booth & Neufer, 2005). As you continue bicycling, your muscles fatigue.

People vary in their percentages of fast-twitch and slow-twitch fibers, for reasons based on both genetics and training. The Swedish ultramarathon runner Bertil Järlaker built up so many slow-twitch fibers in his legs that he once ran 2,188 mi (3,521 km) in 50 days (an average of 1.7 marathons per day) with only minimal signs of pain or fatigue (Sjöström et al., 1987). Contestants in the Primal Quest race have to traverse approximately 500 kilometers (310 miles) by running, mountain climbing, mountain biking, river rafting, and ocean kayaking over 6 to 10 days in summer heat. To endure this ordeal, contestants need many adaptations of their muscles and metabolism, such as increasing numbers of mitochondria (Pearson, 2006). In contrast, competitive sprinters have more fast-twitch fibers and other adaptations for speed instead of endurance (Andersen et al., 1994; Canepari et al., 2005). The best sprinters are not the best marathon runners.

Stop & Check

3. In what way are fish movements impaired in cold water?
4. Duck breast muscles are red ("dark meat"), whereas chicken breast muscles are white. Which species can fly for a longer time before fatiguing, and why?

See page 232 for the answer.

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Muscle Control by Proprioceptors

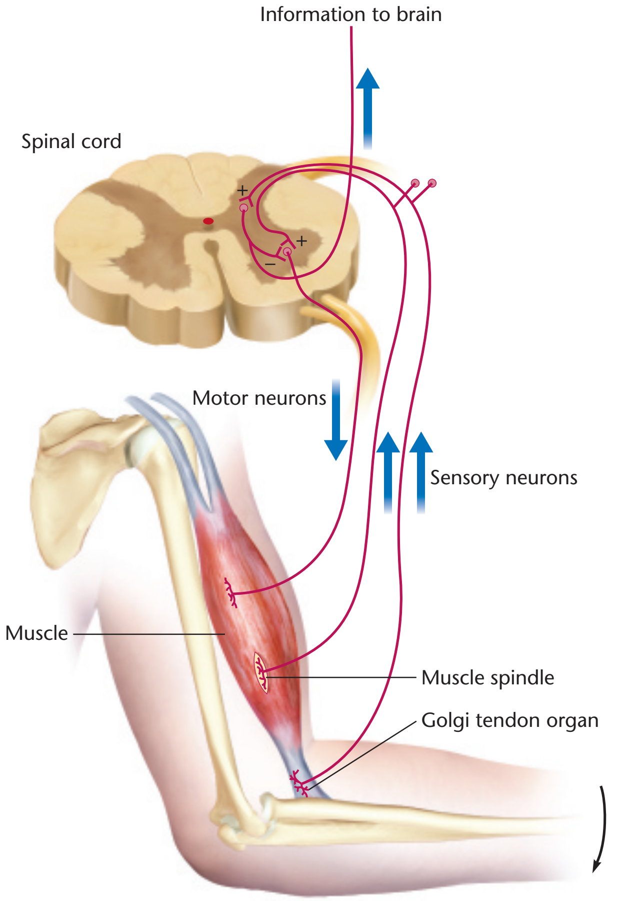
If you walk along a bumpy road, you might set your foot down a little too hard or not quite hard enough. You adjust your posture and maintain your balance without even thinking about it. How do you do that?

A baby is lying on its back. You playfully tug its foot and then let go. At once, the leg bounces back to its original position. How and why?

In both cases, proprioceptors control the movement (Figure 7.5). A **proprioceptor** (from the Latin *proprius*, meaning "one's own") is a receptor that detects the position or movement of a body part—in these cases, a muscle. Muscle proprioceptors detect the stretch and tension of a muscle and send messages that enable the spinal cord to adjust its signals. When a muscle is stretched, the spinal cord sends a signal to contract it reflexively. This **stretch reflex** is *caused* by a stretch; it does not *produce* one.

Figure 7.5 Two kinds of proprioceptors regulate muscle contractions

When a muscle is stretched, nerves from the muscle spindles transmit impulses that lead to contraction of the muscle. Contraction of the muscle stimulates the Golgi tendon organ, which acts as a brake or shock absorber to prevent a contraction that is too quick or extreme.



One kind of proprioceptor is the **muscle spindle**, a receptor parallel to the muscle that responds to a stretch. When the muscle is stretched, the muscle spindle sends a message to a motor neuron in the spinal cord, which in turn sends a message back to the muscle, causing a contraction (Dimitriou, 2014). Note that this reflex provides negative feedback: When a person sets a foot down on a bump on the road, their knee bends a bit, stretching the extensor muscles of that leg. The nerves from the spindles send action potentials to the motor neuron in the spinal cord, which sends action potentials to contract the extensor muscle and straighten the leg.

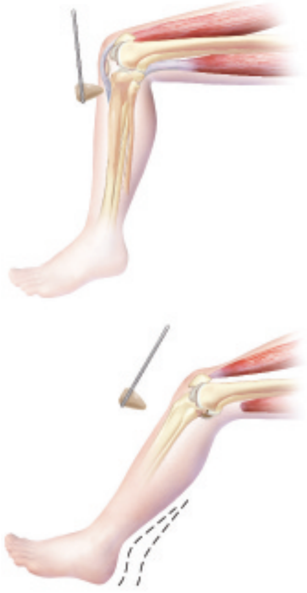
A physician who asks you to cross your legs and then taps just below the knee is testing your stretch reflexes (Figure 7.6). The tap stretches the extensor muscles and their spindles, resulting in a message that jerks the lower leg upward. A leg that jerks excessively or not at all may indicate a neurological problem.

Golgi tendon organs, proprioceptors in the tendons at opposite ends of a muscle, respond to increases in muscle tension. Some muscles are so strong that they could damage themselves if too many fibers contracted at once. Golgi tendon organs detect the tension that results during a muscle contraction, sending messages to the spinal cord to inhibit the motor neurons. In doing so, they put on the brakes to prevent an excessive contraction.

The proprioceptors not only control important reflexes but also provide the brain with information. Here is an illusion that you can try: Find a small, dense object and a larger, less dense object that weighs the same as the

Figure 7.6 The knee-jerk reflex

This is an example of a stretch reflex.



small one. For example, you might try a golf ball and a larger ball of the same weight. Drop one of the objects onto someone's hand while they are watching. (Watching is essential.) Then remove it and drop the other object onto the same hand. Most people report that the small one felt heavier. The reason is that with the larger object, people set themselves up with an expectation of a heavier weight. The actual weight displaces their proprioceptors less than expected and therefore yields the perception of a lighter object. You can get a similar result by asking someone to lift a small, heavy box and a larger box that weighs the same. The smaller box will seem heavier. A general principle is that the brain reacts to sensations that differ from its expectations or predictions (Barrett and Simmons, 2015).

Try It Yourself

Stop & Check

5. If you hold your arm straight out and someone pulls it down slightly, it quickly bounces back. Which proprioceptor is responsible?

6. What is the function of Golgi tendon organs?

See page 232 for the answer.

Units of Movement

Movements include speaking, walking, threading a needle, and throwing a basketball while off balance and evading two defenders. Different kinds of movement need different kinds of control by the nervous system.

Voluntary and Involuntary Movements

Reflexes are consistent automatic responses to stimuli. We generally think of reflexes as *involuntary* because they are insensitive to reinforcements, punishments, and motivations. One example is the stretch reflex, and another is the constriction of the pupils in response to bright light.

Few behaviors are entirely voluntary. When a person walks, which we think of as a voluntary activity, reflexes compensate for the bumps and irregularities in the road. Their arms swing automatically.

Try this: While sitting, raise your right foot and make clockwise circles. Keep your foot moving while you draw the number 6 in the air with your right hand. Or just move your right hand in counterclockwise circles. You will probably reverse the direction of your foot movement. It is difficult to make "voluntary" clockwise and counterclockwise movements on the same side of the body at the same time. However, it is typically much less difficult to move your left hand in one direction while moving the right foot in the opposite direction.

Try It Yourself

Movements Varying in Sensitivity to Feedback

The military distinguishes ballistic missiles from guided missiles. A ballistic missile is launched like a thrown ball: Once it is launched, no one can change its aim. A guided missile detects the target and adjusts its trajectory to correct its aim.

Similarly, some movements are ballistic, and others are corrected by feedback. A **ballistic movement**, such as a reflex, is executed as a whole, but most behaviors are subject to feedback correction. When a person threads a sewing needle, they make a slight movement, check their aim, and then readjust. Similarly, a singer who holds a single note hears any wavering of the pitch and corrects it.

Sequences of Behaviors

Many rapid sequences of behaviors depend on **central pattern generators**, neural mechanisms in the spinal cord that generate rhythmic patterns of motor output. Examples

Alberto Loyo/Shutterstock.com

Nearly all birds reflexively spread their wings when dropped. However, emus—which lost the ability to fly through evolutionary time—do not spread their wings.

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include the mechanisms that generate wing flapping in birds, fin movements in fish, and the "wet-dog shakes." The stimulus that activates a central pattern generator does not control the rhythm of the movements. For example, a cat scratches itself at a rate of three to four strokes per second, regardless of what caused the scratching. Cells in the lumbar segments of the spinal cord generate this rhythm, and they can do so even if they are isolated from the brain or if the muscles are paralyzed (Deliagina et al., 1983).

A fixed sequence of movements is a **motor program**. For example, a mouse periodically grooms itself by sitting up, licking its paws, wiping them over its face, closing its eyes as the paws pass over them, licking the paws again, and so forth. Once begun, the sequence is fixed from beginning to end. Even a mouse without forelimbs goes through the same sequence, so we understand that it does not depend on sensory feedback (Fentress, 1973). A set of cells in the medulla produces this sequence of actions (Xie et al., 2022).

By comparing species, we observe that a motor program can be gained or lost through evolution. If you hold a chicken above the ground and drop it, it extends its wings and flaps them. A chicken with featherless wings makes the same movements, even though the featherless wings will not break the chicken's fall (Provine, 1979, 1981). Chickens, of course, still have the genetic programming to fly. On the other hand, ostriches, emus, and rheas, which have not used their wings for flight in millions of generations, have lost the genes for flight movements and do not flap their wings when dropped (Provine, 1984). (You might pause to think about the researcher who found a way to drop these huge birds to test the hypothesis.)

Do humans have any built-in motor programs? Yawning is one example (Provine, 1986). A yawn includes a prolonged open-mouth inhalation, often accompanied by stretching, and a shorter exhalation. Yawns are consistent in duration, with a mean of just under 6 seconds. Certain facial expressions are also programmed, such as smiles, frowns, and the raised-eyebrow greeting. Hugging is not a built-in motor program, but it is interesting to note that the average nonromantic hug lasts 3 seconds for people throughout the world (Nagy, 2011). Even our voluntary behaviors have a surprising degree of regularity and predictability.

Module 7.1 | In Closing

Categories of Movement

Charles Sherrington described a motor neuron in the spinal cord as "the final common path." He meant that regardless of what sensory and motivational processes occupy the brain, the result is either a muscle contraction or its inhibition. A motor neuron and its associated muscle participate in a great many kinds of movements, and we need many brain areas to control them.

Summary

1. Vertebrates have smooth, skeletal, and cardiac muscles. **226**
2. All vertebrate nerve–muscle junctions use acetylcholine as their neurotransmitter. **226**
3. Skeletal muscles range from slow muscles that do not fatigue to fast muscles that fatigue quickly. We recruit the fast muscles for brief, strenuous activity. **228**
4. Proprioceptors are receptors sensitive to the position and movement of a part of the body. Muscle spindles and Golgi tendon organs help regulate muscle movements. **229**
5. Some movements, especially reflexes, proceed as a unit, with little if any guidance from sensory feedback. Other movements, such as threading a needle, are redirected by sensory feedback. **230**
6. Central pattern generators produce fixed sequences of behaviors with a fixed rhythm. **230**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary.

aerobic	**228**
anaerobic	**228**
antagonistic muscles	**226**
ballistic movement	**230**
cardiac muscles	**226**
central pattern generators	**230**
extensor	**226**
fast-twitch fibers	**228**
flexor	**226**

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Golgi tendon organs **229**
motor program **231**
muscle spindle **229**
neuromuscular junction **226**
proprioceptor **229**
reflexes **230**
skeletal (striated) muscles **226**
slow-twitch fibers **228**
smooth muscles **226**
stretch reflex **229**

Thought Question

Would you expect jaguars, cheetahs, and other great cats to have mostly slow-twitch, nonfatiguing muscles in their legs or mostly fast-twitch, quickly fatiguing muscles? What kinds of animals might have mostly the opposite kind of muscles?

Stop & Check Answers

1. Each axon to eye muscles contracts only about three fibers, as opposed to a hundred or more for axons to the biceps.
2. No, the only input to a skeletal muscle is acetylcholine, which causes it to contract. The only way to oppose a skeletal muscle is to contract its antagonistic muscle.
3. Although a fish can move rapidly in cold water, it fatigues easily.
4. Ducks can fly great distances. The white muscle of a chicken breast has the power necessary to get a heavy body off the ground, but it fatigues rapidly.
5. The muscle spindle
6. Golgi tendon organs respond to muscle tension and prevent excessively strong muscle contractions.

Module 7.1 | End-of-Module Quiz

1. Why can people move eye muscles more precisely than their biceps?
   - **a.** The eye muscles are fast-twitch fibers.
   - **b.** The eye muscles respond to a different neurotransmitter.
   - **c.** The eye muscles have a higher ratio of axons to muscle fibers.
   - **d.** More of the brain is devoted to vision than to movement.

2. After acetylcholine causes a flexor muscle to move a person's hand toward their shoulder, what would move it in the other direction?
   - **a.** A different transmitter causes the muscle to relax.
   - **b.** A different transmitter causes the muscle to move the other direction.
   - **c.** Acetylcholine causes the extensor muscle to contract.
   - **d.** A different transmitter causes the extensor muscle to contract.

3. What happens to a fish's movement speed in colder water?
   - **a.** The fish swims more slowly.
   - **b.** The fish swims at the same speed by making each muscle contract more strongly.
   - **c.** The fish swims at the same speed by recruiting more muscle fibers.
   - **d.** The fish swims faster.

4. Which of the following is true of mammals' fast-twitch muscle fibers?
   - **a.** Because they are aerobic, they are subject to rapid fatigue.
   - **b.** Because they are anaerobic, they are subject to rapid fatigue.
   - **c.** Because they are aerobic, they do not fatigue rapidly.
   - **d.** Because they are anaerobic, they do not fatigue rapidly.

5. A muscle spindle and a Golgi tendon organ are both described as what?
   - **a.** Optic receptors
   - **b.** Metabolic receptors
   - **c.** Proprioceptors
   - **d.** Chemoreceptors

6. What determines the rhythm of a cat's scratching movements, or the wet-dog shakes?
   - **a.** The rhythm of activity produced by the stimulus itself
   - **b.** The structure of the muscles
   - **c.** Commands from the prefrontal cortex
   - **d.** A set of neurons in the spinal cord

Answers: 1c, 2c, 3c, 4b, 5c, 6d.

Module 7.2

Brain Mechanisms of Movement

Learning Objectives

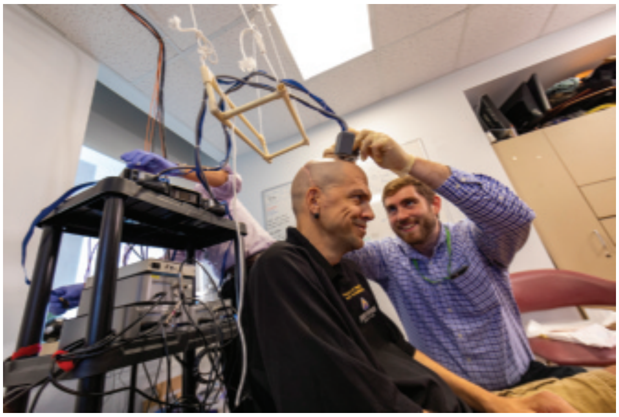
After studying this module, you should be able to:

4. Contrast the roles of several cortical areas in the control of movement.
5. Discuss the role of the prefrontal cortex in inhibiting movements.
6. Evaluate the concept of mirror neurons.
7. Contrast the anatomy and functions of the lateral and medial corticospinal tracts.
8. Describe the functions of the cerebellum and basal ganglia.
9. Evaluate the evidence regarding the role of consciousness in planning a movement.

Why do we care how the brain controls movement? One goal is to help people who have spinal cord damage or limb amputations. Suppose we could listen in on their brain messages and decode what movements they would like to make. Then biomedical engineers could route those messages to muscle stimulators or robotic limbs. Sound like science fiction? Not really. Researchers implanted an array of microelectrodes into the motor cortex of a woman who was paralyzed from the neck down. Then they connected electrodes in her primary motor cortex to a robotic arm, enabling her to make simple reaching and grasping movements (Hochberg et al., 2012). A man who became quadriplegic after a diving accident gradually learned to use his brain activity to control a device that stimulated muscles in his arm (Figure 7.7). For example, he learned to pick up a bottle and pour it into a cup (Bouton et al., 2016).

Figure 7.7

A patient with a C6 spinal cord injury connected to a computer reading data of brain activity captured by six implanted electrodes. This patient is able to control 2 robotic arms that can cut his food and raise it to his mouth.



John Hopkins University/Craig Weiman

However, the technology has limitations. Electrodes implanted into the brain can drift out of position and damage neurons. Using electroencephalogram (EEG) instead of implanted electrodes is safer but less precise, nevertheless providing enough information to control very slow walking (Selfslagh et al., 2019). A compromise is to place a grid of electrodes on the surface of the brain without penetrating it (Lebedev and Nicolelis, 2019). Still, as Miguel Nicolelis (2003) has pointed out, progress will require both improved brain-machine interfaces (BMIs) and a better understanding of the brain.

Miguel Nicolelis (b. 1961)

Ultimately, I believe that the design of a successful BMI for restoring control of upper limb movements will have to take into account general physiological principles of how motor signals underlying these movements are encoded in the primate brain. (Nicolelis, 2003)

The Cerebral Cortex

Since the pioneering work of Gustav Fritsch and Eduard Hitzig (1870), neuroscientists have known that direct electrical stimulation of the **primary motor cortex**—the precentral gyrus of the frontal cortex, just anterior to the central sulcus (Figure 7.8)—elicits movements. Axons from the motor cortex do not go directly to the muscles, but to the brainstem and spinal cord, which send impulses to the muscles (Kinoshita et al., 2012). Although each hemisphere mainly controls the muscles on the contralateral side, both hemispheres contribute to planning movements on both sides (Bundy et al., 2018).

Controlling movement also depends on connections between the cortex and subcortical areas, as illustrated in Figure 7.9. Don't get bogged down in details of the figure at this point. We shall attend to each area in due course.

The cerebral cortex is necessary for complex actions such as talking or writing, but not for coughing, sneezing, gagging, laughing, or crying (Rinn, 1984). The lack of cerebral control may explain why it is hard to perform those actions voluntarily. The primary motor cortex is also active when you imagine movements, remember movements, or understand verbs related to movements (Tomasino and Gremese, 2016). To understand words like *run*, *walk*, or *stumble*, you have to imagine doing them.

Figure 7.10 (which repeats parts of Figure 3.23) depicts which areas of the somatosensory cortex feel parts of the body, and which areas of the motor cortex control parts of the body. A key point is the similarity between the two. The motor cortex is just anterior to the somatosensory cortex, and the two match up nicely. You need to feel a body part to control its movement accurately. Within any area of the motor cortex, the organization represents coordinated movements, not just single muscle contractions. For example, some of the cells in the hand area control grasping movements and others control movements to release a grip (Huber et al., 2020).

For many years, researchers studied the motor cortex in laboratory animals by stimulating neurons with brief electrical pulses, usually less than 50 milliseconds (ms) in duration, producing brief muscle twitches. Later researchers found different results when they lengthened the pulses to half a second. Instead of twitches, they elicited complex

Figure 7.8 Principal motor areas of the human cortex

The primary motor cortex provides most of the output to the brainstem and spinal cord.

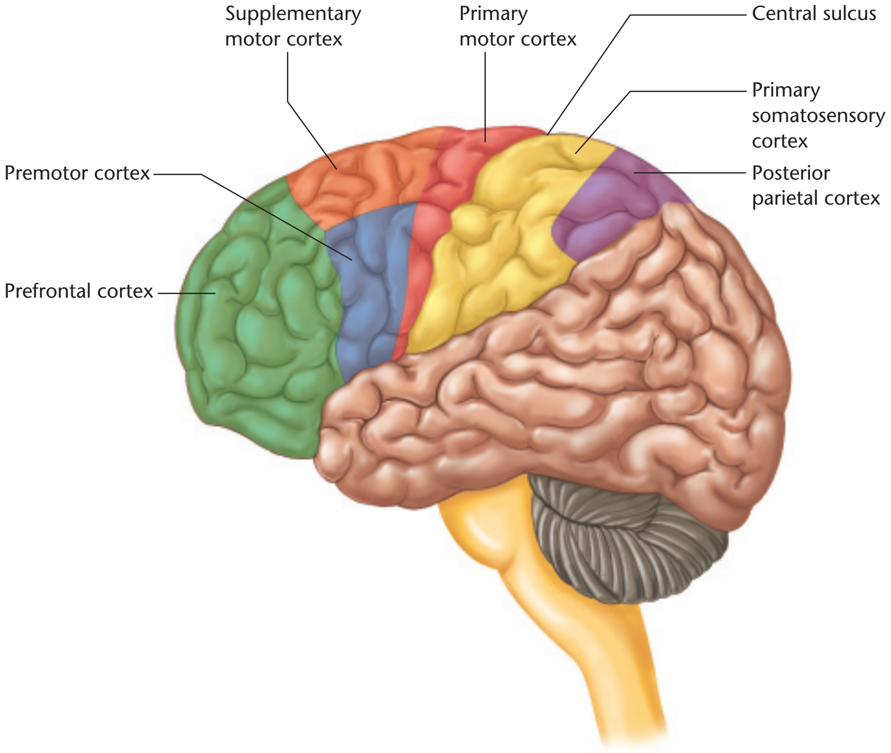

Supplementary motor cortex
Primary motor cortex
Central sulcus
Primary somatosensory cortex
Premotor cortex
Posterior parietal cortex
Prefrontal cortex

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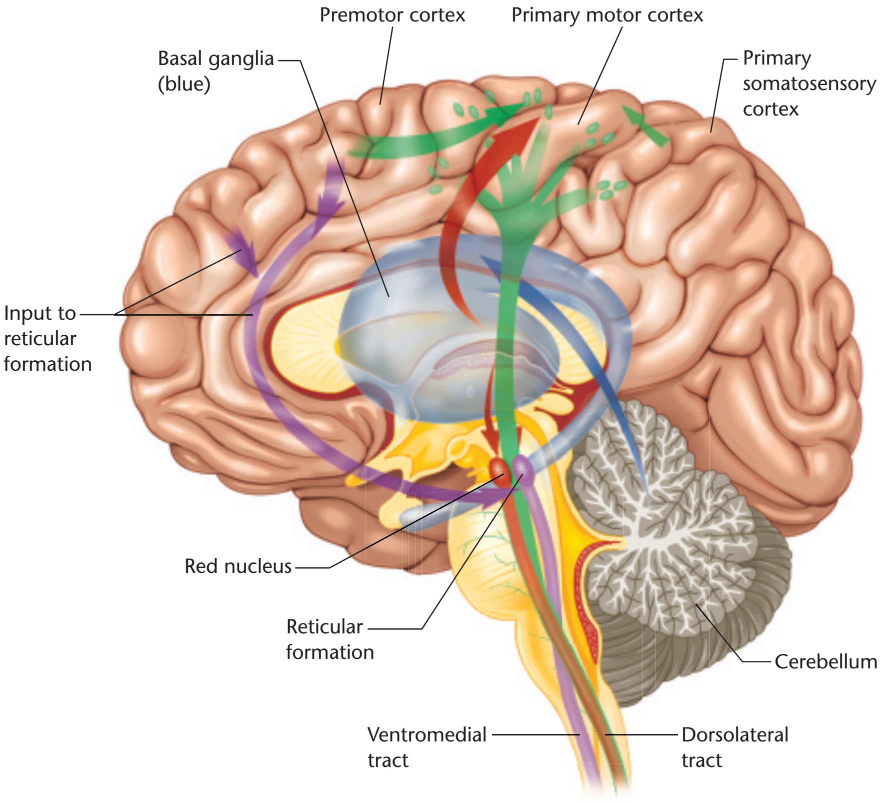
Figure 7.9 Motor control in mammals

Paths from the primary motor cortex, other cortical areas, and midbrain control motor neurons in the medulla and spinal cord, which control muscles.



movement patterns. Stimulation of one spot caused a monkey to make a grasping movement with its hand, move its hand to just in front of the mouth, and open its mouth—as if it were picking up something and preparing to eat it (Graziano et al., 2002). Repeated stimulation of this spot elicited the same result each time, regardless of the initial position of the monkey's hand. That is, the stimulation produced a certain *outcome*, not a particular *movement*. The motor cortex orders an outcome and leaves it to the spinal cord and other areas to find the right combination of muscles (Scott, 2004).

Stop & Check

7. What aspect of brain anatomy facilitates communication between body sensations and body movements?
8. What evidence indicates that cortical activity represents the goal of the movement and not just the muscle contractions?

See page 247 for the answer.

Planning a Movement

Physicians sometimes perform brain surgery on people who are awake, anesthetizing only the skin of the scalp. (The brain itself has no pain receptors.) During the surgery, physicians can briefly stimulate brain areas and record the results (with the patient's permission). When they stimulate parts of the **posterior parietal cortex** (Figure 7.8), people frequently report an *intention* to move—such as an intention to move the left hand. After more intense stimulation at the same locations, people report that they believe they *did* make the movement—although, in fact, they did not (Desmurget et al., 2009).

Researchers sometimes use fMRI to measure brain responses while people are preparing to make a movement. The details vary, but the general idea is that people detect a first signal that tells them what they are supposed to do, and then they wait for a second signal that indicates make the movement now. Or people see a first signal with partial information about what they will have to do, and after a

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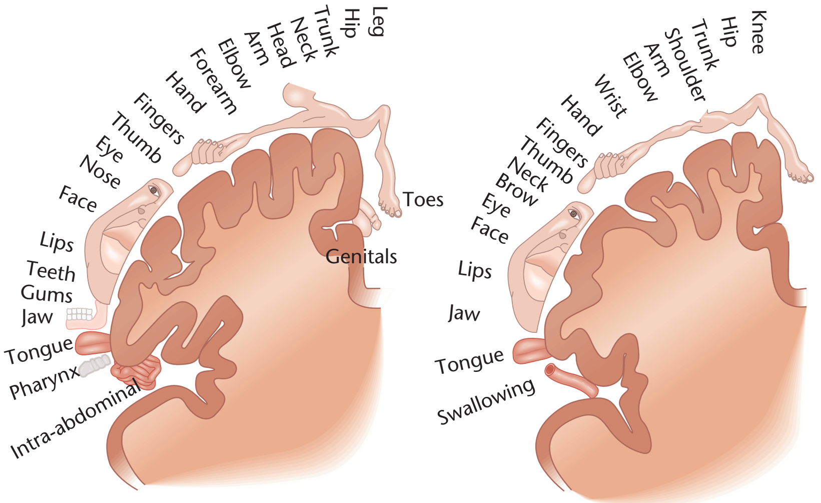
Figure 7.10 Coronal section through the primary somatosensory cortex and primary motor cortex

The motor cortex lies just anterior to the somatosensory cortex. The motor area responsible for moving a certain body part is aligned with the somatosensory area responsible for feeling that body part.



(a) Somatosensory cortex (b) Motor cortex

(**Source:** Adapted from Penfield and Rasmussen, 1950)

delay a second signal tells them more precisely what to do. In each case, the posterior parietal cortex is active during the delay, evidently preparing the movement (Hesse et al., 2006; Lindner et al., 2010).

The **supplementary motor cortex** in the prefrontal cortex is also essential for planning and organizing movements. After mild electrical stimulation of the supplementary motor cortex, people report an urge or desire to make a movement, and after stronger stimulation, they actually make a movement (Fried et al., 1991). From that observation we might assume that the supplementary motor cortex controls the intention or desire, but another finding argues otherwise: After damage to the area, people at first have only few and slight voluntary movements, but they report that they did not lack the desire to move. They simply could not get a movement started (Sjoberg, 2021). Activity in the supplementary motor cortex begins at least a second before the start of a voluntary movement and builds up gradually (Fried et al., 2011). It is also essential for inhibiting a habitual movement when you want to do something else, and for learning to correct errors of movement (Bonini et al., 2014; Isoda and Hikosaka, 2007).

The **premotor cortex** is most active immediately before a movement. It receives information about the target to which the body is directing its movement, as well as information about the body's current position and posture (Hoshi and Tanji, 2000). Both kinds of information are necessary to direct a movement toward a target. When you imagine how a movement would feel, you activate your premotor cortex (Zabicki et al., 2019).

Parts of the **prefrontal cortex** are important for considering the probable outcomes of movements (Tucker et al., 1995). If you had damage to this area, many of your movements would be disorganized, such as showering with your clothes on or pouring water on the tube of toothpaste instead of the toothbrush (Schwartz, 1995). Interestingly, this area is inactive during dreams, and the actions we dream about doing are often as illogical as those of people with prefrontal cortex damage (Braun et al., 1998; Maquet et al., 1996). If you do something absentminded first thing in the morning, probably your prefrontal cortex is not fully awake.

Stop & Check

9. If someone electrically stimulated the posterior parietal cortex or the supplementary motor cortex, how would the results be similar, and how would they differ?
10. If someone's movements seem disorganized and illogical, what type of brain damage might be responsible?

See page 247 for the answer.

Inhibiting a Movement

Consider what happens when you need to restrain an impulse. The traffic light changes from red to green, but just as you are about to drive forward, you hear an ambulance siren telling you to stay out of the way. Or you start to swing at a tennis ball in a doubles match when your partner shouts, "let it go," because it will land out of bounds.

In cases like these, two brain areas are sending competing messages, and the outcome depends on whether the stop message arrives in time to cancel the action message (Schmidt et al., 2013).

Another example—not an important behavior for its own sake, but a convenient one for psychologists to study—is the **antisaccade task**. A saccade (sa-KAHD) is a voluntary eye movement from one target to another. Suppose a person is staring straight ahead when something to one side or the other moves. They have a strong tendency to look toward the moving object. In the antisaccade task, you are supposed to look as quickly as possible in the *opposite* direction. Try it yourself: Hold one hand to the left of someone's head and the other hand to the right. When you wiggle a finger, the person is instructed to look at the *other* hand. Or have someone do the same for you. People generally agree that it is easier to look at the finger that moved than the finger that didn't.

Try It Yourself

Before age 5 to 7 years, most children find it almost impossible to look away from the wiggling finger. Ability to perform this task gradually improves as the prefrontal cortex matures (Bucci and Seessau, 2012). Performing the antisaccade task requires activity in the prefrontal cortex and basal ganglia *before* seeing the wiggling finger (Velanova et al., 2009; Watanabe and Munoz, 2010). That is, the brain prepares to inhibit the unwanted action and substitute a different one. Performance declines in old age and as a result of schizophrenia, attention-deficit disorder, or alcohol intoxication (Bansal et al., 2021; Lee et al., 2015; Loe et al., 2009; Maurage et al., 2021; Munoz and Everling, 2004; Plomecka et al., 2020).

Stop & Check

11. How does the antisaccade task measure activity of the prefrontal cortex?

See page 247 for the answer.

Mirror Neurons

A discovery in neuroscience that excited many psychologists was **mirror neurons**, which are active both during a movement and while watching someone else perform the same movement (Rizzolatti and Sinigaglia, 2010). Mirror neurons were first reported in the premotor cortex of monkeys (Gallese et al., 1996) and later in other areas and other species, including humans (Dinstein et al., 2007; Kilner et al., 2009). For example, certain neurons become active both when people smile and when they see someone else smile (Montgomery et al., 2009). The theoretical interest comes from the possibility that we use mirror neurons to understand other people or to identify with them. One speculation was that a lack of mirror neurons might be responsible for autism or schizophrenia, disorders associated with deficient social relationships. However, researchers found normal mirror neurons in both conditions (Andrews et al., 2015; Dinstein et al., 2010).

If mirror neurons are going to explain imitation or empathy, the mirror neurons would have to come first. Could we be born with neurons that already knew that moving a particular muscle corresponds to seeing someone else make a particular movement? The question is, do mirror neurons *cause* imitation and social behavior, or do they *result from* them?

The only evidence for inborn mirror neurons came from reports that some newborn infants imitate certain adult facial expressions, such as tongue protrusion. That result suggests built-in mirror neurons that connect the sight of a movement to the movement itself (Meltzoff and Moore, 1977). However, infants are difficult to test, and the investigators decide what facial movements do or do not count as imitations. One extensive study reported that infants' expressions and gestures did not match what they see any more often than we would expect by chance (Oostenbroek et al., 2016). A review of the literature over decades found that six research groups have reported positive findings, whereas 10 groups have not (Slaughter, 2021). The claim of infant imitation behavior is controversial and uncertain.

Several observations demonstrate that mirror neurons form through learning. Mirror neurons are activated not only by seeing an action but also by any reminder of the action, such as hearing an action or reading about it (Foroni and Semin, 2009; Kohler et al., 2002; Ricciardi et al., 2009; Speer et al., 2009). In an interesting experiment, researchers asked people to watch a display on the screen and move their index finger whenever the hand on the screen moved the little finger. They were to move their little finger whenever the hand on the screen moved the index finger. After some practice, these "mirror" neurons turned into "counter-mirror" neurons that responded to moving one finger and watching a different finger (Catmur et al., 2007). In short, it seems likely that mirror neurons need to learn their properties after interacting with others.

Stop & Check

12. When expert pianists listen to familiar, well-practiced music, they imagine the finger movements, and the finger area of their motor cortex becomes active, even if they are not moving their fingers (Haueisen and Knösche, 2001). If we regard those neurons as another kind of mirror neuron, what do these results imply about the origin of mirror neurons?

See page 247 for the answer.

From the Brain to the Spinal Cord

Messages from the brain must reach the medulla and spinal cord, which control the muscles. Paths from the cerebral cortex to the spinal cord are called the **corticospinal tracts**. We have two such tracts, the lateral and medial corticospinal tracts. Both tracts contribute to nearly all movements,

Table 7.1 | Disorders of the Spinal Cord

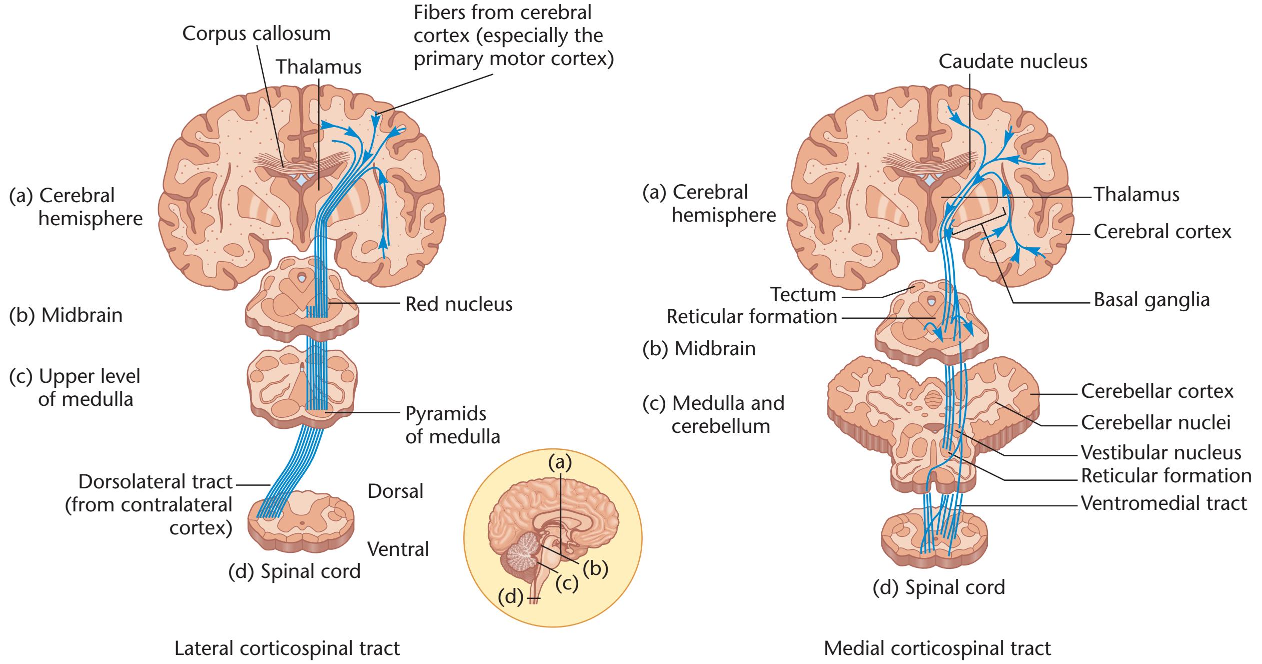
Disorder	Description	Cause
Paralysis	Loss of voluntary movement in part of the body	Damage to motor neurons or their axons in the spinal cord
Paraplegia	Loss of sensation and voluntary muscle control in the legs (Genital stimulation can produce orgasm, despite the lack of conscious sensation.)	A cut through the spinal cord in the thoracic region or lower
Quadriplegia (or tetraplegia)	Loss of sensation and voluntary muscle control in both arms and legs	Cut through the spinal cord in the cervical (neck) region
Hemiplegia	Loss of sensation and voluntary muscle control in the arm and leg of either the right or left side	Cut halfway through the spinal cord
Tabes dorsalis	Impaired sensations and muscle control in the legs and pelvic region, including bowel and bladder control	Damage to the dorsal roots of the spinal cord in the late stage of syphilis
Poliomyelitis	Paralysis	A virus that damages motor neurons in the spinal cord
Amyotrophic lateral sclerosis	Gradual weakness and paralysis, starting with the arms and spreading to the legs	Gradual loss of motor neurons

although a movement may rely on one tract more than the other. Diseases of the spinal cord impair movement, as listed in Table 7.1.

The **lateral corticospinal tract** extends from the primary motor cortex, nearby areas of the cortex, and the **red nucleus**, a midbrain area especially important for arm muscles (Figure 7.11). In bulges of the medulla called *pyramids*, the lateral tract crosses to the contralateral side of the spinal cord. (For that reason, the lateral tract is also called the pyramidal tract.) It controls movements in peripheral

Figure 7.11 The corticospinal tracts

The lateral corticospinal tract crosses to the opposite side of the spinal cord and controls precise movements of the extremities, such as hands, fingers, and feet. The medial corticospinal tract controls trunk muscles for bilateral movements such as standing, bending, turning, and walking.


Corpus callosum
Thalamus
Fibers from cerebral cortex (especially the primary motor cortex)
(a) Cerebral hemisphere
(b) Midbrain
Red nucleus
(c) Upper level of medulla
Pyramids of medulla
Dorsolateral tract (from contralateral cortex)
Dorsal
Ventral
(d) Spinal cord
(a)
(b)
(c)
(d)
Caudate nucleus
(a) Cerebral hemisphere
Thalamus
Cerebral cortex
Tectum
Reticular formation
Basal ganglia
(b) Midbrain
(c) Medulla and cerebellum
Cerebellar cortex
Cerebellar nuclei
Vestibular nucleus
Reticular formation
Ventromedial tract
(d) Spinal cord

Lateral corticospinal tract

Medial corticospinal tract

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areas, especially the hands and feet on the contralateral side of the body. Fibers from the somatosensory cortex modify the movement based on sensory information (Karadimas et al., 2020).

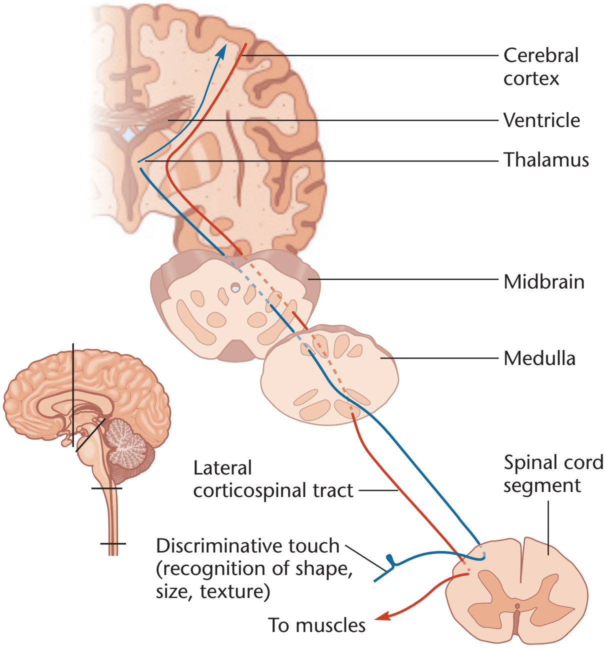
The **medial corticospinal tract** extends from many areas of the cerebral cortex, as well as from several areas of the midbrain and medulla (Figure 7.11). Axons of the medial tract go to both sides of the spinal cord about equally, where they control the muscles of the neck, shoulders, and trunk and therefore movements as walking, turning, bending, standing up, and sitting down (Kuypers, 1989). You may be able to move your fingers on just one side of the body, but movements such as standing, sitting, or turning necessarily include both sides.

An easy way to remember the functions of the lateral and medial tracts is that the lateral tract controls muscles in the lateral parts of the body, such as hands and feet. The medial tract controls muscles in the medial parts of the body, including trunk and neck.

Figure 7.11 compares the lateral and medial corticospinal tracts. Figure 7.12 compares the lateral tract to the spinal pathway bringing touch information to the cortex. Note that both paths cross in the medulla and that the touch information arrives at brain areas side by side with those areas responsible for motor control. Touch is obviously essential for movement. For a person to control their hands, they have to know where they are and what they are doing now.

Figure 7.12 The touch path and the lateral corticospinal tract

Both paths cross in the medulla so that each hemisphere has access to the opposite side of the body. The touch path goes from touch receptors toward the brain; the corticospinal tract goes from the brain to the muscles.


Cerebral cortex
Ventricle
Thalamus
Midbrain
Medulla
Lateral corticospinal tract
Spinal cord segment
Discriminative touch (recognition of shape, size, texture)
To muscles

If a stroke damages the primary motor cortex of one hemisphere, the result is impaired movement on the other side of the body. Eventually, depending on the location and amount of damage, the person may regain some muscle control from spared axons in the lateral tract or from the small amount of ipsilateral control by the opposite hemisphere. Sometimes the medial tract can approximate the intended movement. For example, someone with impaired control of the hand muscles might move the shoulders and trunk in a way that repositions the hand.

Stop & Check

13. What kinds of movements does the lateral tract control? The medial tract?

See page 247 for the answer.

The Cerebellum

The term *cerebellum* is Latin for "little brain." Decades ago, most texts described the function of the cerebellum as "balance and coordination." Well, yes, people with cerebellar damage do lose balance and coordination, but that description understates the importance of this structure. The cerebellum has more neurons than the rest of the brain combined (Williams and Herrup, 1988), a huge number of synapses, and many functions. It receives input from the cerebral cortex, especially the frontal and parietal lobes, and relays information back to modify cortical activity (Gao et al., 2018; Marek et al., 2018).

The cerebellum is essential for any behavior that relates to aim or precise timing of short intervals. People with cerebellar damage can accurately judge the loudness of a sound, but not its duration. If a sound predicts a puff of air to the eyes one second later, people with cerebellar damage learn the connection between the events, but they cannot produce the eyeblink at the appropriate time. They are impaired at tapping a rhythm, clapping hands, judging which visual stimulus moved faster, and judging which delay between tones was longer (Ivry and Diener, 1991; Keele and Ivry, 1990).

They are also impaired at nearly all athletic activities that require aim or timing. Researchers have found larger than average cerebellums in college basketball players (Park et al., 2009), competitive speed skaters (Park et al., 2012), and world-class mountain climbers (Di Paola et al., 2013). We do not know whether the enlargement is the cause or the result of skillful activity.

Here is a quick way to test the cerebellum: Hold up your hands and ask someone to look at one hand and then quickly look to the other hand. Someone with cerebellar damage has difficulty programming the angle and distance

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of eye movements (Dichgans, 1984). The eyes make many short movements until, by trial and error, they eventually find the intended spot.

In the *finger-to-nose test*, someone is instructed to hold one arm straight out and then, at command, touch the nose as quickly as possible. A normal person does so in three steps. First, the finger moves ballistically to a point just in front of the nose. This *move* function depends on the cerebellar cortex (the surface of the cerebellum), which sends messages to the **cerebellar nuclei** (clusters of cell bodies) in the interior of the cerebellum (Figure 7.13). Second, the finger remains steady at that spot for a fraction of a second. This *hold* function depends on the nuclei alone (Kornhuber, 1974). Finally, the finger moves to the nose by a slower movement that does not depend on the cerebellum. Someone with damage to the cerebellar cortex has trouble with the initial rapid movement. The finger misses the nose, stops too soon, or goes too far. Someone with damage to the cerebellar nuclei has difficulty with the hold segment: The finger reaches a point in front of the nose and then wavers.

Try It Yourself

The symptoms of cerebellar damage resemble those of alcohol intoxication: clumsiness, slurred speech, and inaccurate eye movements. A police officer testing someone for drunkenness may use the finger-to-nose test or similar tests because the cerebellum is one of the first brain areas that alcohol affects.

Cellular Organization

The cerebellum receives input from the spinal cord, from the sensory systems, and from the cerebral cortex. Processing in the cerebellum finally reaches the cerebellar nuclei, which send output back to the cerebral cortex as well as to downstream targets (Figure 7.14).

Figure 7.14 Connections of the cerebellum

Input from all areas of the cerebral cortex reaches the pons, which relays information to granule cells of the cerebellum. Output from the cerebellar nuclei returns to the cortex by way of the thalamus.

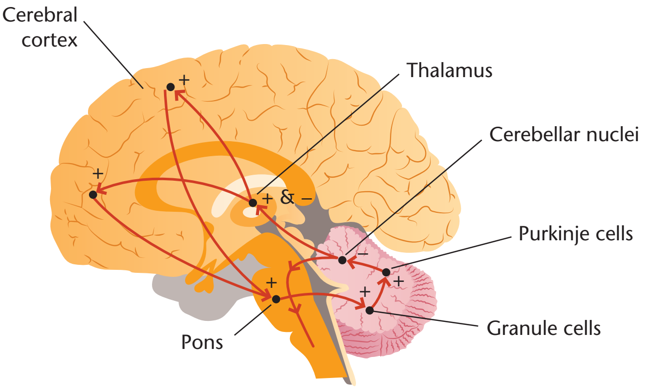
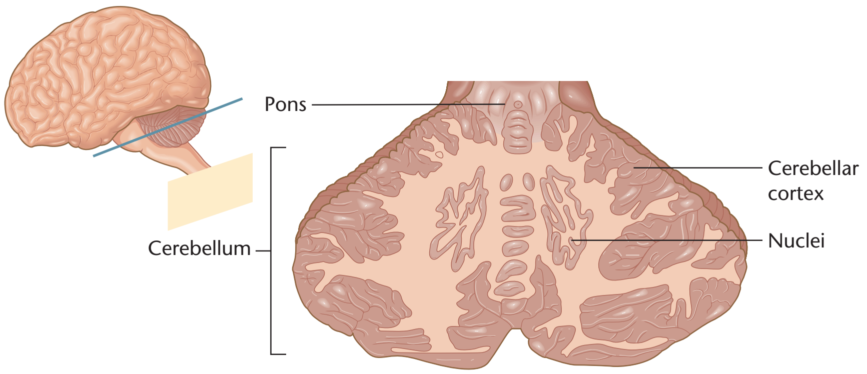


Figure 7.15 is a simplified diagram of neurons in the cerebellum. Here are the key points:

- The neurons are arranged in a precise geometrical pattern, with multiple repetitions of the same units.
- The **Purkinje** (pur-KIN-jee) **cells** are flat (two-dimensional) cells in sequential planes, parallel to one another.
- The **parallel fibers** are axons parallel to one another and perpendicular to the planes of the Purkinje cells.
- Action potentials in parallel fibers excite one Purkinje cell after another. Each Purkinje cell then transmits an inhibitory message to cells in the cerebellar nuclei, which provide the output to the thalamus and midbrain.
- Depending on which and how many parallel fibers are active, they might stimulate only the first few Purkinje cells or a long series of them. Because the parallel fibers'

Figure 7.13 Location of the cerebellar nuclei relative to the cerebellar cortex

In the inset at the upper left, the line indicates the plane depicted in detail at the lower right.



messages reach Purkinje cells one after another, the greater the number of excited Purkinje cells, the longer their collective response lasts. If the parallel fibers stimulate only the first few Purkinje cells, the message from the Purkinje cells is brief, and if the parallel fibers stimulate more Purkinje cells, the message lasts longer (Their et al., 2000).

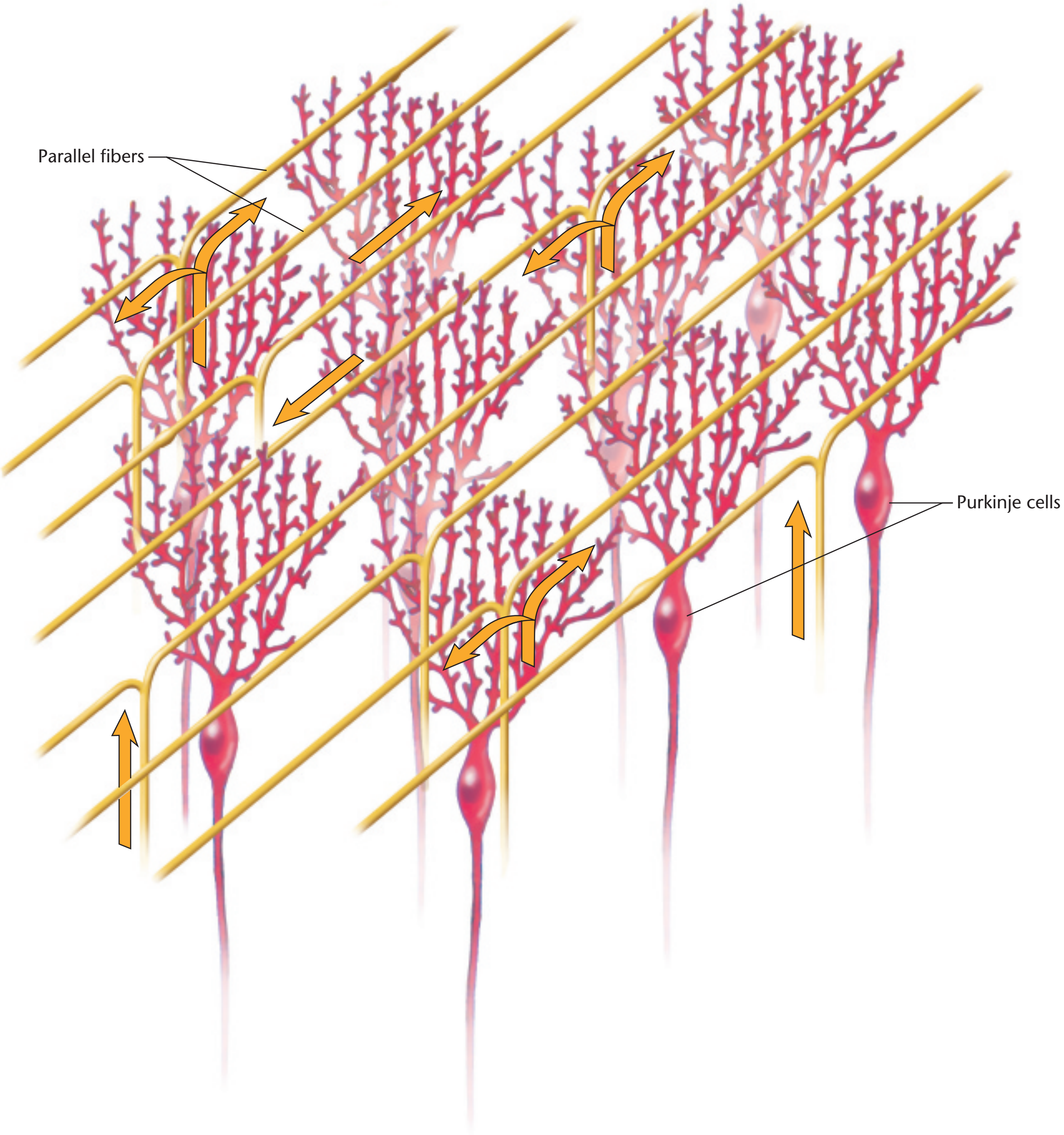
Stop & Check

14. How are the parallel fibers arranged relative to one another and to the Purkinje cells?
15. If a larger number of parallel fibers are active, what is the effect on the collective output of the Purkinje cells?

See page 247 for the answer.

Figure 7.15 A cellular circuit in the cerebellum

Parallel fibers (yellow) activate one Purkinje cell after another. Purkinje cells (red) inhibit a target cell in one of the nuclei of the cerebellum (not indicated, but found toward the bottom of the illustration). The more Purkinje cells that respond, the longer the target cell is inhibited. In this way, the cerebellum controls the duration of a movement.



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Functions Other than Movement

Traditionally, the cerebellum has been emphasized for its role in movement, but it has reciprocal connections with all parts of the cerebral cortex, enabling it to contribute to almost everything the brain does (Diedrichsen et al., 2019). The chapter on learning and memory will discuss the role of the cerebellum in classical conditioning.

The cerebellum is critical for certain aspects of attention. In one study, people were told to keep their eyes fixated on a central point. At various times, they would see the letter E on either the left or right half of the screen, and they were to indicate the direction in which it was oriented (E, Ǝ, Ш, or ᗰ) without moving their eyes. Sometimes, they saw a signal telling where the letter would be on the screen. For most people, that signal improved their performance even if it appeared just 100 ms before the letter. For people with cerebellar damage, the signal had to appear nearly a second before the letter to be helpful. Evidently, they needed longer to shift their attention (Townsend et al., 1999).

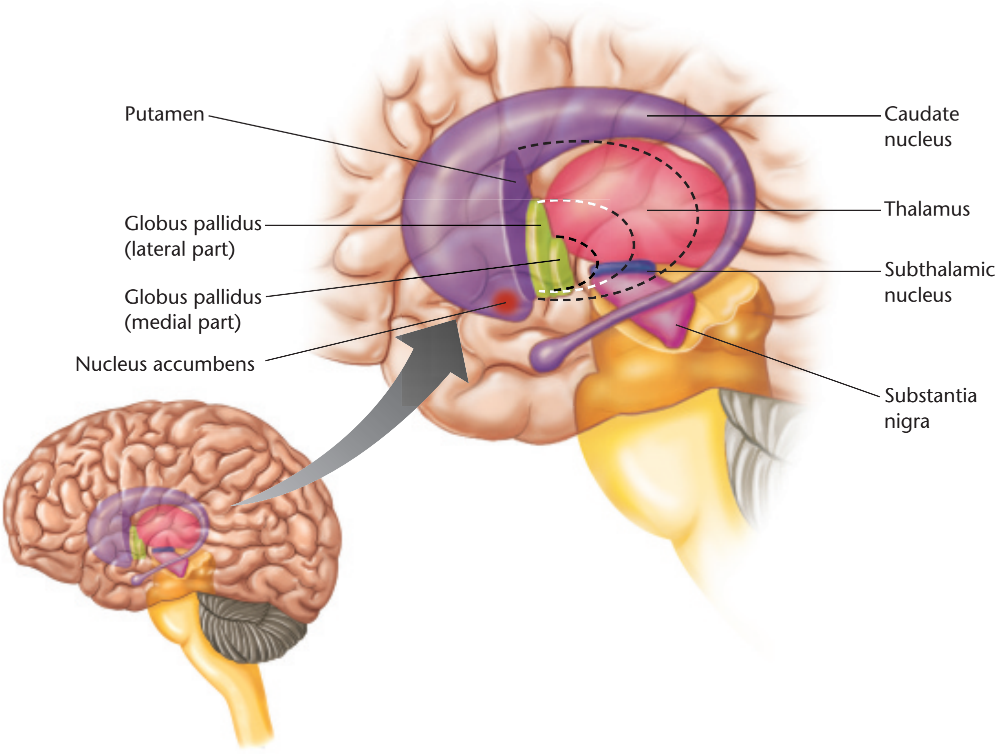
Because the circuit diagram of cells in the cerebellum is nearly uniform throughout, researchers and theorists have tried to describe a single function for the cerebellum, but so far without notable success. The cerebellum contributes to many tasks that have little to do with one another. Perhaps it is no more reasonable to seek "the" function of the cerebellum than to seek "the" function of the cerebral cortex (Diedrichsen et al., 2019).

The Basal Ganglia

The term **basal ganglia** applies to the subcortical forebrain structures illustrated in Figure 7.16. (*Ganglia* is the plural of *ganglion*.) These structures include the caudate nucleus, the putamen (pyuh-TAY-men), the globus pallidus, and the nucleus accumbens. The caudate nucleus and putamen together form the **striatum** or **dorsal striatum**. The striatum receives input from the cerebral cortex and substantia nigra and sends output to the globus pallidus, which then sends output to the thalamus and frontal cortex (Saunders et al., 2015). The striatum also sends output back to the

Figure 7.16 Location of the basal ganglia

The basal ganglia surround the thalamus and are surrounded by the cerebral cortex.



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substantia nigra, which has connections to much of the brain (McElvain et al., 2021).

Figure 7.17 illustrates the direct and indirect pathways of the basal ganglia. The direct pathway from the striatum inhibits the globus pallidus, which inhibits part of the thalamus. By inhibiting an inhibitor, the net effect is excitation. Neuroscientists long believed that the direct pathway stimulates movements whereas the indirect pathway inhibits them. However, later evidence found that both pathways are active before a movement and neither is active when the animal is at rest (Calabresi et al., 2014; Cui et al., 2013). A popular hypothesis is that the direct pathway enhances the selected movement whereas the indirect pathway inhibits competing movements (Cox and Witten, 2019; Kravitz et al., 2012). The hyperdirect pathway, not depicted in Figure 7.17, goes from the cerebral cortex to the subthalamic nucleus to the globus pallidus. This path inhibits actions quickly, when it is important to change plans suddenly (Mosher et al., 2021). Imagine a person is driving forward when the traffic light turns green, but then a dog darts in front of the car. When they quickly hit the brakes, it is the hyperdirect path that enables them to do so.

The basal ganglia are particularly important for spontaneous, self-initiated behaviors. For example, a monkey in one study was trained to move a hand left or right to receive food. In trials when it heard a signal indicating exactly when to move, the basal ganglia exhibited little activity. In other trials the monkey saw a signal to start a movement in not less than 1.5 seconds and not more than 3 seconds. Thus, the monkey had to choose its own starting time. Under those conditions, the basal ganglia were highly active (Turner and Anderson, 2005).

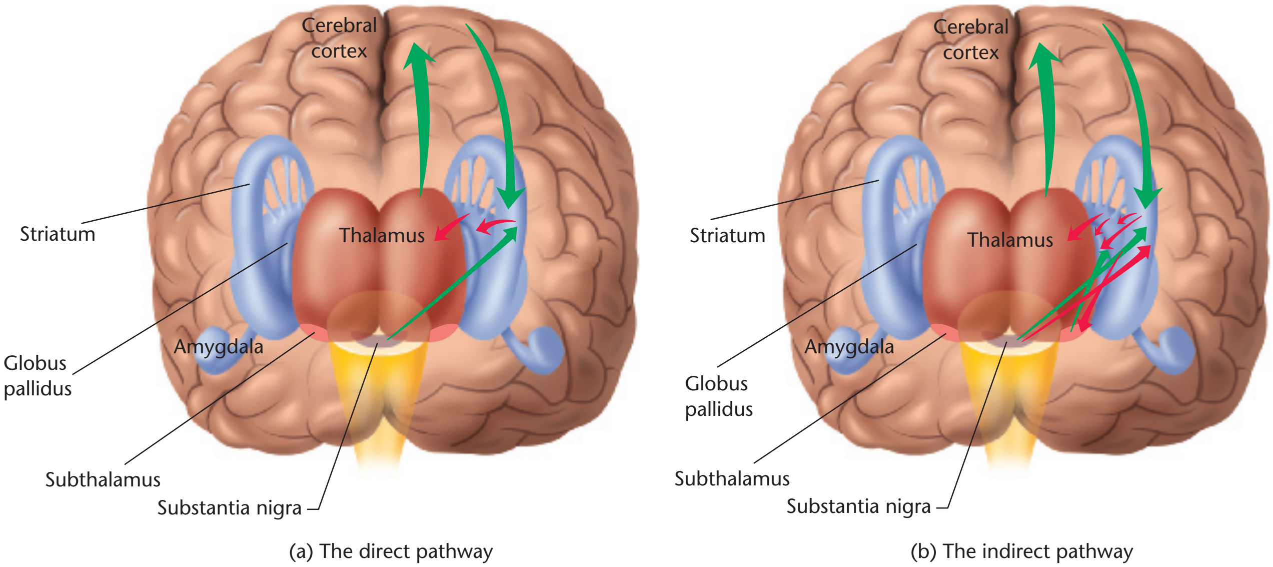
In another study, people used a computer mouse to draw lines on a screen while researchers used PET scans to examine brain activity. Activity in the basal ganglia increased when people drew a new line but not when they traced a line already on the screen (Jueptner and Weiller, 1998). Again, the basal ganglia seem critical for self-initiated actions, not for stimulus-elicited actions.

Self-initiated behaviors have a slower onset than those in response to a stimulus. If someone shouts, "Time for dinner," you get up at once and head for the table. But if you are thinking about getting a snack, you ponder for a while before you slowly get up to go. If you raise your hand to ask a question in class, ordinarily you think about it for a while before you slowly raise your hand. But if the professor asks how many students want to postpone the next test, you might raise your hand at once.

The difference between stimulus-initiated and self-initiated behaviors has an interesting consequence. Many old Western movies included a gunfight between the hero and the villain. The villain always drew his gun first, but even though the hero started later, he won the draw. Researchers wondered, is that realistic? Could someone draw second and still win? The answer is yes, and in some cases the person drawing second might even have an advantage, because a reaction to a stimulus (seeing the other person go for his gun) is faster than a spontaneous movement. In one

Figure 7.17 Two pathways through the basal ganglia

The indirect pathway has extra connections within the globus pallidus and back and forth to the subthalamus.



(a) The direct pathway

(b) The indirect pathway

experiment, two people had a competition. While watching each other, they had to wait an unpredictable period of time—if they acted too soon, the results didn't count—and then press three buttons in a particular order (analogous to drawing a gun and shooting). The person who finished the buttons first was the winner. So, each person sometimes initiated the action and sometimes reacted after seeing the other person act. On average, when people were reacting to the other person's act, they made the movements 9 percent faster (Welchman et al., 2010). A replication found similar results (La Delfa et al., 2013). So, you just learned something useful for the next time you get into a gunfight.

Because cells in the primary motor cortex become active before those in the basal ganglia, the basal ganglia must not be responsible for selecting which movement to make. Rather, their role is to regulate the vigor of the movement (Turner and Desmurget, 2010). Many cells in the basal ganglia cells respond strongly to signals indicating that a response will probably lead to reward. Stimulating them produces the same effects as increasing the reward (Ikemoto et al., 2015; Tai et al., 2012). Separate sections of the basal ganglia respond to the recent value associated with a stimulus and the long-term average value associated with it (Hikosaka et al., 2018). Cells in the basal ganglia store long-term memories of the reward value of many objects, more than 90 in one study (Ghazizadeh and Hikosaka, 2021).

After damage to the striatum, animals move weakly, and increasing the reward does not increase their response vigor (da Silva et al., 2018; Wang et al., 2013). Describing the role of the basal ganglia in these terms makes sense of what we see in patients with damage to the basal ganglia, as in Parkinson's disease. They sometimes move reasonably well in response to signals, but their spontaneous movements are slow and weak, as if they felt little motivation. Remember, the basal ganglia control mainly self-initiated movements.

The basal ganglia are also critical for learning new habits (Yin and Knowlton, 2006). When you are first learning to drive a car, you attend carefully to everything you do, but later it becomes so habitual that you hardly think about it. People with basal ganglia damage are impaired at learning motor skills and converting them into smooth, automatic responses (Poldrack et al., 2005; Willingham et al., 1996).

Stop & Check

16. The basal ganglia have their predominant effect on what type of movements?
17. Which aspect of movement do the basal ganglia control?
18. What type of learning depends on the basal ganglia?

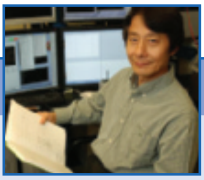
See page 247 for the answer.

Conscious Decisions and Movement

Where does consciousness come into all of this? Each of us has the feeling, "I consciously decide to do something, and then I do it." It seems so obvious that we might not even question it, but research casts doubt on this assumption.

Imagine yourself in the following study (Libet et al., 1983). You are instructed to flex your wrist whenever you choose. You don't choose which movement to make, but you choose the time freely. You should not decide in advance when to move but let an urge occur as spontaneously as possible. The researchers take three measurements. First, they attach electrodes to your scalp to record evoked electrical activity over your motor cortex. Second, they attach a sensor to record when your hand starts to move. Third, they take your self-report: You watch a clocklike device, as depicted in Figure 7.18, in which a spot of light moves around the circle every 2.56 seconds. Do not decide in advance that you will flex your wrist at a particular time, but when you do decide to move, note where the spot of light is at that moment, and remember it to report it later.

The procedure starts. You think, "Not yet . . . not yet . . . not yet . . . NOW!" You note where the spot was at that critical instant and report, "I made my decision when the light was at position 25." The researchers compare your report to their records of your brain activity and your wrist movement. On the average, people report that their decision to move occurred about 200 ms before the actual movement. (The *decision* occurred then. People *report* it later.) For example, if you reported that your decision to move occurred at position 25, your decision came 200 ms before the movement that began at position 30. (Remember, the light moves around the circle in 2.56 seconds.) However, your motor cortex produces a kind of activity called a



Okihide Hikosaka (b. 1948)

We may choose particular objects deliberately or automatically. Are the deliberate and automatic choices controlled by different brain mechanisms? Do they work independently? If so, how is the final choice made? One of our research projects is focused on the functions of the basal ganglia which seem to be involved in most of the above functions. (https://irp.nih.gov/pi/okihide-hikosaka)

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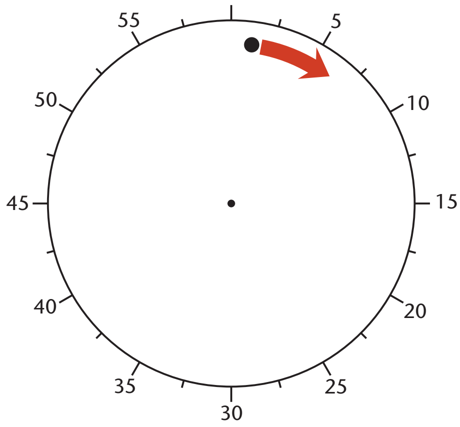
Figure 7.18 Procedure for Libet's study of conscious decision and movement

The participant was to make a spontaneous decision to move the wrist and remember where the light was at the time of that decision.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(**Source:** From "Time of conscious intention to act in relation to onset of cerebral activities (readiness potential): The unconscious initiation of a freely voluntary act," by B. Libet et al., in *Brain, 106*, pp. 623–42. Reprinted by permission of Oxford University Press.)

readiness potential for any voluntary movement, and on average, the readiness potential begins at least 500 ms before the movement. In this example, it would start when the light was at position 18, as illustrated in Figure 7.19.

The results vary among individuals, but most are similar. The key point is that the brain activity responsible for the movement begins before the reported decision! The results seem to indicate that your conscious decision does not cause your action. Rather, you become conscious of the decision after the process leading to action has been underway for about 300 milliseconds.

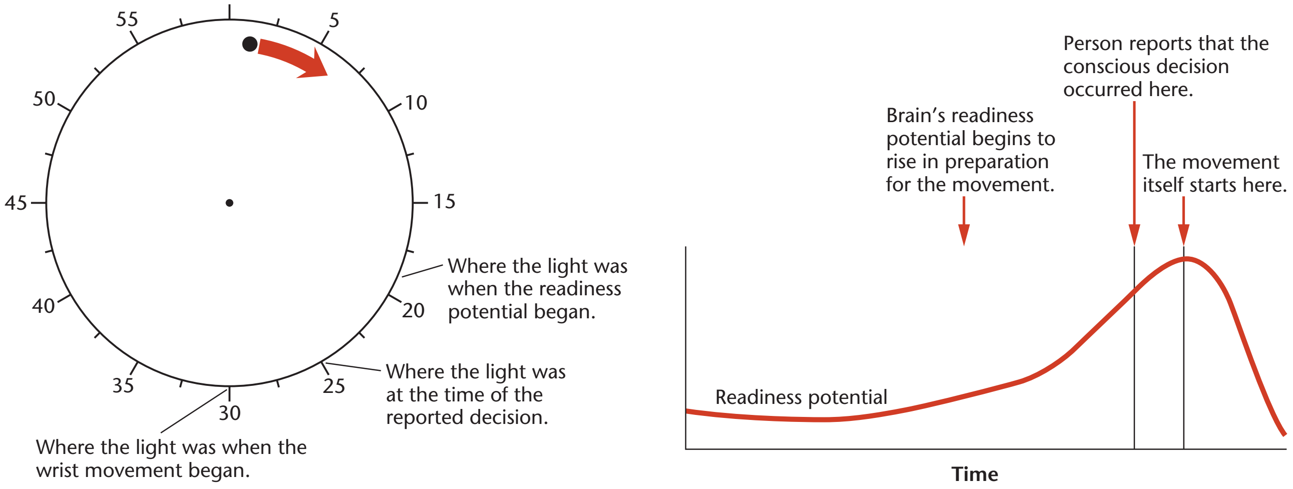
As you can imagine, this experiment has sparked much discussion among philosophers as well as psychologists. The research has been replicated in other laboratories, so the results are solid (e.g., Lau et al., 2004; Trevena and Miller, 2002). One study found that some neurons in the supplementary motor cortex begin activating more than a second before the reported time of the decision (Fried et al., 2011).

We also know that when people are asked to report the time of a sensory stimulus, or the time that they made a movement (instead of the decision to move), their estimates are usually within 30 to 50 ms of the correct time (Lau et al., 2004; Libet et al., 1983). They are not exactly right, but they are close. Many have assumed that if people can accurately state the time of a stimulus or a movement, they are equally accurate at stating the time of a conscious decision. But maybe they are not.

Consider another experiment: Imagine you are watching a screen that displays letters of the alphabet, one at a time, changing every half-second. In this case you choose not just when to act, but which of two acts to do. You should decide at some point whether to press a button on the left or one on the right. When you make that decision, press the button immediately, and remember what letter was on the screen when you decided which button to press. Meanwhile, the researchers record activity from your cortex. The result: People usually report a letter they

Figure 7.19 Results from study of conscious decision and movement

On average, the brain's readiness potential began at least 300 ms before the reported decision, which occurred 200 ms before the movement.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Where the light was when the readiness potential began.
Where the light was at the time of the reported decision.
Where the light was when the wrist movement began.
Person reports that the conscious decision occurred here.
Brain's readiness potential begins to rise in preparation for the movement.
The movement itself starts here.
Readiness potential
Time

(**Source:** From "Time of conscious intention to act in relation to onset of cerebral activities (readiness potential): The unconscious initiation of a freely voluntary act," by B. Libet et al., in *Brain, 106*, pp. 623–42. Reprinted by permission of Oxford University Press.)

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saw within one second of making the response. Remember, the letters changed only twice a second, so it wasn't possible to determine the time of decision with great accuracy. However, it wasn't necessary, because parts of the frontal and parietal cortices showed activity specific to the left or right hand *7 to 10 seconds* before the response (Soon et al., 2008). Someone monitoring your cortex could, in this situation, predict your choice a few seconds before you were aware of making the decision.

This second experiment calls attention to the fact that the decision in this type of experiment forms gradually. Nevertheless, your brain activity does not always start 7 to 10 seconds before you make a movement. If it did, no baseball player would ever hit a pitch, and no tennis player would ever return a serve. Your responses to signals are fast, and only your self-initiated responses are slow.

In both of the experiments described here, the procedure asks you to state exactly when you made a voluntary decision, as if it happened at a single moment. In fact, it develops gradually, because the movement is self-initiated, the type that depends on the basal ganglia (Guggisberg and Mottaz, 2013). When you report the time of the decision, it may be little more than a guess (Banks and Isham, 2009; Rigoni et al., 2010). Reporting when you decided to make a voluntary movement is like reporting when you fell in love with someone: You know when you were sure of it, or when you first said, "I love you," but the process was developing gradually long before that.

The implication is that a conscious decision is gradual. It begins with a process that builds up to a certain level before you are sure about it.

Stop & Check

19. Explain the evidence suggesting that a conscious decision to move does not cause the movement.
20. What makes this evidence difficult to interpret?

See page 247 for the answer.

Module 7.2 | In Closing

Movement Control and Cognition

It is tempting to describe behavior in three steps—first we perceive, then we think, and finally we act. Brain activities do not fall into those neat categories. The cerebellum has traditionally been considered a major part of the motor system, but it is now known to be important in timing sensory processes. People with basal ganglia damage are slow to start a movement, and they are also slow at making any kind of choice. Organizing a movement is not something we tack on at the end of our thinking. It is intimately intertwined with all of our sensory and cognitive processes. The study of movement is not just the study of muscles. It is the study of how we decide what to do.

Summary

1. The cortex sends input to the medulla and spinal cord, which have axons to control the muscles. **234**
2. Each area of the motor cortex is closely aligned with a portion of the somatosensory cortex that pertains to the same body part. **234**
3. The primary motor cortex produces patterns representing the intended outcome, not just the muscle contractions. **234**
4. Areas near the primary motor cortex—including the prefrontal, premotor, and supplementary motor cortices—are active in preparing for a movement. **236**
5. The ability to inhibit an inappropriate behavior develops gradually in children and adolescents, depending on maturation of the prefrontal cortex and basal ganglia. **236**
6. Mirror neurons in various brain areas respond to both a self-produced movement and an observation of a similar movement by another individual. In many, possibly all, cases they are a result of learning to identify with others, rather than a cause of it. **237**
7. The lateral tract has axons that cross to the opposite side of the spinal cord, controlling peripheral muscles such as those of the hands and feet. The medial tract controls bilateral movements near the midline of the body. **237**
8. The cerebellum is critical for movements that require accurate aim and timing, as well as for attention and many other processes. **239**
9. The cells of the cerebellum are arranged in a regular pattern that enables them to produce outputs of precisely controlled duration. **240**

10. The basal ganglia are large subcortical structures that are important for self-initiated behaviors. They are important for the motivation and vigor of responses. **242**
11. When people state the instant when they formed a conscious intention to move, their time precedes the actual movement by about 200 ms but follows the start of motor cortex activity by about 300 ms. It is not clear how accurately people can report the time of a conscious decision. A voluntary decision to move develops gradually, not suddenly. **244**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary.

antisaccade task **237**
basal ganglia **242**
cerebellar nuclei **240**
corticospinal tracts **237**
lateral corticospinal tract **238**
medial corticospinal tract **239**
mirror neurons **237**
parallel fibers **240**
posterior parietal cortex **235**
prefrontal cortex **236**
premotor cortex **236**
primary motor cortex **234**
Purkinje cells **240**
readiness potential **245**
red nucleus **238**
striatum or dorsal striatum **242**
supplementary motor cortex **236**

Thought Question

Human infants are at first limited to gross movements of the trunk, arms, and legs. The ability to move one finger at a time matures gradually over at least the first year. What hypothesis would you suggest about which brain areas controlling movement mature early and which areas mature later?

Stop & Check Answers

7. The area of motor cortex devoted to a particular body structure is aligned with the somatosensory cortex area responsive to the same structure.
8. Activity in the motor cortex leads to a particular outcome, such as movement of the hand to the mouth, regardless of the hand's current location.
9. Mildly stimulating either one elicits an intention or desire to make a movement. Stronger stimulation of the supplementary motor cortex produces an actual movement, but strong stimulation of the posterior parietal cortex produces an illusion of having made a movement.
10. Damage in the prefrontal cortex.
11. The task measures the ability to inhibit an impulse, and inhibition depends on the prefrontal cortex.
12. These neurons must have acquired these properties through experience. They developed as pianists learned to copy what they hear.
13. The lateral tract controls detailed movements in the periphery, mainly on the contralateral side of the body. The medial tract controls trunk movements bilaterally.
14. The parallel fibers are parallel to one another and perpendicular to the planes of the Purkinje cells.
15. As a larger number of parallel fibers become active, the Purkinje cells increase their duration of response.
16. The basal ganglia have more influence on self-initiated movements, which are generally slower.
17. The basal ganglia control the vigor of movements.
18. The basal ganglia are essential for learning motor habits.
19. Researchers recorded responses in people's cortex that predicted the upcoming response. Those brain responses occurred earlier than the time people reported as "when they made the decision."
20. The studies assume that people accurately report the times of their intentions, but we cannot be confident of their accuracy. A decision to make a voluntary movement is a gradual process that cannot be pinpointed to a single instant.

Module 7.2 | End-of-Module Quiz

1. The motor cortex sends its axons to what target?
   - **a.** The medulla and spinal cord
   - **b.** The muscles
   - **c.** The thalamus
   - **d.** The autonomic nervous system

2. Which of these would be most likely to occur after damage to the supplementary motor cortex?
   - **a.** Loss of reflexive movements
   - **b.** Difficulty starting a movement
   - **c.** Loss of motivation for movement
   - **d.** Delusions of having made movements that actually did not occur

3. What does the antisaccade task measure?
   - **a.** The ability to inhibit a movement
   - **b.** The ability to vary the strength of a movement
   - **c.** The ability to control the speed of a movement
   - **d.** The ability to alternate between antagonistic muscles

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4. To conclude that mirror neurons help people imitate, what would someone have to demonstrate?
   - **a.** Mirror neurons respond to both seeing and hearing someone else's movement.
   - **b.** Mirror neurons occur in the same brain areas of humans as in monkeys.
   - **c.** Mirror neurons have different properties for people from different cultures.
   - **d.** Mirror neurons develop their properties before children start to imitate.

5. What does the lateral corticospinal tract control?
   - **a.** Bilateral movements of the trunk of the body
   - **b.** Contralateral movements of the trunk of the body
   - **c.** Bilateral movements of the arms, hands, and feet
   - **d.** Contralateral movements of the arms, hands, and feet

6. What does the medial corticospinal tract control?
   - **a.** Bilateral movements of the trunk of the body
   - **b.** Contralateral movements of the trunk of the body
   - **c.** Bilateral movements of the arms, hands, and feet
   - **d.** Contralateral movements of the arms, hands, and feet

7. Which structure contains more than half of the brain's neurons?
   - **a.** Prefrontal cortex
   - **b.** Cerebellum
   - **c.** Thalamus
   - **d.** Basal ganglia

8. Inaccurate saccades and problems on the finger-to-nose test imply probable dysfunction of which structure?
   - **a.** Basal ganglia
   - **b.** Cerebellum
   - **c.** Prefrontal cortex
   - **d.** Primary motor cortex

9. How are the parallel fibers arranged relative to the Purkinje cells?
   - **a.** They are parallel to them.
   - **b.** They are perpendicular to them.
   - **c.** They are arranged at random angles.
   - **d.** They circle around each Purkinje cell.

10. The cerebellum has reciprocal connections with what?
    - **a.** Nearly all parts of the cerebral cortex
    - **b.** Motor neurons of the spinal cord
    - **c.** Hypothalamus
    - **d.** Sympathetic nervous system

11. The basal ganglia are most important for which type of movements?
    - **a.** Stimulus-triggered movements, which are generally fast
    - **b.** Stimulus-triggered movements, which are generally slow
    - **c.** Self-initiated movements, which are generally fast
    - **d.** Self-initiated movements, which are generally slow

12. In what way, if at all, does basal ganglia activity relate to motivation?
    - **a.** The basal ganglia increase vigor of response depending on expected reward value.
    - **b.** The basal ganglia help to maintain constant behavior even when motivation is low.
    - **c.** The basal ganglia become active only when you are competing against someone else.
    - **d.** Basal ganglia activity has nothing to do with motivation.

13. According to Libet's study, what is the order of events in a voluntary movement?
    - **a.** People form an intention, then activity begins in the premotor cortex, and finally the movement starts.
    - **b.** People form an intention at the same time when activity begins in the premotor cortex, and a bit later, the movement starts.
    - **c.** Activity begins in the premotor cortex, a bit later, people are aware of forming an intention, and finally the movement starts.
    - **d.** Activity begins in the premotor cortex, and a bit later, people are aware of forming an intention, and simultaneously the movement starts.

Answers: 1a, 2b, 3a, 4d, 5d, 6a, 7b, 8b, 9b, 10a, 11d, 12a, 13c.

Module 7.3

Movement Disorders

Learning Objectives

After studying this module, you should be able to:

10. Discuss the causes and treatment of Parkinson's disease.

11. Describe the genetics of Huntington's disease.

If you have damage in your spinal cord, peripheral nerves, or muscles, you cannot move, but cognitively you are the same as ever. In contrast, brain disorders that impair movement also impair mood, memory, and cognition. We consider two examples: Parkinson's disease and Huntington's disease.

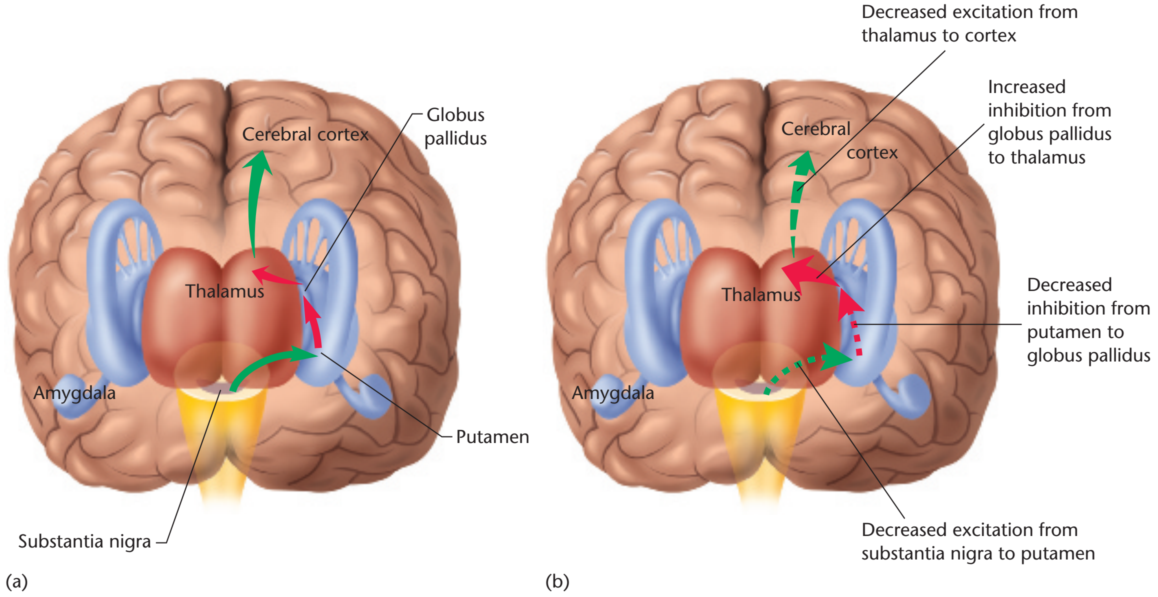
Parkinson's Disease

Parkinson's disease results from the gradual loss of dopamine-releasing axons going from the substantia nigra to the striatum. It is one particular pathway from a genetically defined type of dopamine neuron in a limited portion of the substantia nigra (Kamath et al., 2022). After this loss of input, the striatum decreases its inhibition of the globus pallidus, which therefore increases its inhibitory input to the thalamus, as depicted in Figure 7.20. Parkinson's disease is a *progressive* disease—one that gradually progresses to a worse and worse outcome. It affects more than 1 percent of people over age 60, with increasing prevalence at higher ages.

The symptoms include rigidity, muscle tremors, slow movements, and difficulty initiating voluntary activity. People with Parkinson's disease sometimes move normally in response to signals or instructions, such as while following a parade (Teitelbaum et al., 1991), but their spontaneous, self-initiated movements are slow and weak. They also experience difficulty with inhibiting inappropriate movements (Jahanshahi et al., 2015). These symptoms are consistent with the role of the striatum for choosing, planning,

Figure 7.20 Connections from the substantia nigra: (a) normal and (b) in Parkinson's disease

Excitatory paths are shown in green; inhibitory are in red. Decreased excitation from the substantia nigra decreases inhibition from the striatum, leading to increased inhibition from the globus pallidus. The net result is decreased excitation from the thalamus to the cortex.


Cerebral cortex
Globus pallidus
Thalamus
Amygdala
Putamen
Substantia nigra
(a)
Decreased excitation from thalamus to cortex
Cerebral cortex
Increased inhibition from globus pallidus to thalamus
Thalamus
Decreased inhibition from putamen to globus pallidus
Amygdala
Decreased excitation from substantia nigra to putamen
(b)

(**Source:** Based on Yin and Knowlton, 2006)

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and motivating movements, and for inhibiting unwanted ones. Many, but not all, Parkinson's patients may experience depression (Martínez-Horta et al., 2014), and many have problems with attention, language, or memory (Miller et al., 2013).

Causes

The problem starts in the substantia nigra, but what causes the damage to the substantia nigra? Early-onset Parkinson's disease (usually defined as before age 40 to 50) has high heritability, but the far more common late-onset condition has lower heritability (Tanner et al., 1999; Thacker and Ascherio, 2008). Researchers have identified genes that can cause early-onset Parkinson's disease, and many genetic variants that slightly raise the risk of late-onset Parkinson's disease (Li et al., 2021; Nalls et al., 2014). One rare gene with a substantial effect impairs the function of mitochondria (Lin et al., 2020). Having a brother or sister with the condition increases the risk more than does having a parent or child with the condition (Liu et al., 2018; Thacker and Ascherio, 2008). The genetic similarity is the same, but brother and sister have their early environment in common. One study found many cases in which both husband and wife developed Parkinson's disease (Liu et al., 2018). Husband and wife have environmental similarity without genetic similarity. The pattern of results indicates that genes contribute to the risk, but factors in the environment might be even more important, especially for late-onset Parkinson's. Possibly the genes increase vulnerability to environmental insults.

An accidental discovery implicated exposure to toxins as another factor in Parkinson's disease (Ballard et al., 1985). In northern California in 1982, several young adults developed symptoms of Parkinson's disease after using a drug with effects similar to heroin. Before the investigators could alert the community to the danger, many other users had developed symptoms ranging from mild to fatal (Tetrud et al., 1989). The substance responsible for the symptoms was **MPTP**, a chemical that the body converts to **MPP$^+$**, which accumulates in, and then destroys, neurons that release dopamine[1] (Kim-Han et al., 2011; Nicklas et al., 1992).

No one supposes that Parkinson's disease often results from using recreational drugs, but much research suggests increased risk among workers with much exposure to pesticides (e.g., farmers) or metals (welders and miners) (Chambers-Richards, 2021). Several studies have found increased prevalence of the disease in areas with greater air pollution (Dorsey et al., 2021). Exposure to harmful chemicals increases the risk especially among people with any of the genes that predispose to Parkinson's (Cannon and Greenamyre, 2013). If someone also had a traumatic head injury, the risk goes up even more (P.C. Lee et al., 2012). In short, most cases result from a combination of influences.

What might decrease the risk of Parkinson's disease? When researchers compared the lifestyles of people who did and didn't develop the disease, they found that people who smoke cigarettes or drink coffee or tea have less chance of developing Parkinson's disease (Li et al., 2015; Ritz et al., 2007). (Consider that sentence again.) One study took questionnaire results from more than a thousand pairs of young adult twins and compared the results to medical records decades later. Of the twins who had never smoked, 18.4 percent developed Parkinson's disease. In contrast, 13.8 percent of the smokers developed the disease, as did only 11.6 percent of the heaviest smokers (Wirdefeldt et al., 2005). Needless to say, cigarettes increase the danger of lung cancer and other diseases more than they decrease the risk of Parkinson's disease. Coffee and tea are safer. Exercise helps also (Belvisi et al., 2020; Hong et al., 2020). Nicotine, caffeine, and exercise are all ways of stimulating the brain. Still, in each case, the mechanism of decreasing Parkinson's risk is uncertain.

Stop & Check

21. How do the symptoms of Parkinson's disease relate to the functions of the striatum?
22. What lifestyle factors increase or decrease the risk of Parkinson's disease?

See page 254 for the answer.

L-Dopa Treatment

Because Parkinson's disease results from a dopamine deficiency, a logical goal is to restore the missing dopamine. A dopamine pill would be ineffective because dopamine does not cross the blood–brain barrier. Physicians in the 1950s and 1960s reasoned that **L-dopa**, a precursor to dopamine that does cross the barrier, might be a good treatment. In contrast to all the medicines that were discovered by trial and error, this was the first drug in psychiatry or neurology, and one of the first in all of medicine, to emerge from a plausible theory. Taken as a daily pill, L-dopa reaches the brain, where neurons convert it to dopamine, partially restoring movement and other behaviors. L-dopa is still the most common treatment for Parkinson's disease. Other treatments include drugs that directly stimulate dopamine receptors and drugs that block the metabolic breakdown of dopamine.

However, these treatments have limitations. They are more effective in some people than in others, probably because of variation in the intestinal bacteria that metabolize L-dopa before it can enter the blood (Rekdal et al., 2019). They tend to become less effective over time. The side effects are usually tolerable, but they can include nausea, restlessness, sleep problems, low blood pressure, repetitive movements, and sometimes hallucinations and delusions. A few patients develop unrestrained behaviors, such as impulsive gambling, eating, shopping, or sex (Drew et al., 2020; Wylie et al., 2012). The most important limitation is that although replacing lost

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[1] The full names of these chemicals are 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenylpyridinium ion. (Let's hear it for abbreviations.)

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dopamine reduces the symptoms of Parkinson's disease, it does not halt the continuing progressive damage.

Non-pharmaceutical Therapies

If dopamine replacement becomes ineffective or unsatisfactory, physicians sometimes implant electrodes to stimulate the subthalamic nucleus or the globus pallidus. The stimulation facilitates desired movements and inhibits unintended movements (de Hemptinne et al., 2015; Mosher et al., 2021). One hypothesis is that people with Parkinson's disease have excessive synchrony of firing in the basal ganglia, and the stimulation breaks up unhealthy rhythms (David et al., 2020).

The limitation has been that continuous brain stimulation drains the battery attached to the electrodes. Basic research on the basal ganglia revealed that the electrical stimulation stimulates two types of neurons with different effects. Researchers then found that a series of short bursts of stimulation could excite one type of neuron while inhibiting the other type, resulting in benefits that lasted for more than two hours after the end of stimulation. That pattern would drain the battery more slowly. So far, this procedure has been tried only with laboratory mice, but it has much potential for use with humans (Spix et al., 2021).

A potentially exciting strategy has been "in the experimental stage" for decades. In a pioneering study, M. J. Perlow and colleagues (1979) injected the chemical 6-OHDA (6-hydroxydopamine, a chemical modification of dopamine) into rats to damage the substantia nigra of one hemisphere, producing Parkinson's-type symptoms on the opposite side of the body. After the movement abnormalities stabilized, the experimenters transplanted substantia nigra tissue from rat fetuses into the damaged brains. Most recipients recovered much of their normal movement within four weeks. Control animals that suffered the same brain damage without receiving grafts showed little or no recovery. This is only a partial brain transplant, but still, the Frankensteinian implications are striking.

If such surgery works for rats, might it also for humans? Ordinarily, scientists test any experimental procedure extensively with laboratory animals before trying it on humans, but with Parkinson's disease, the temptation was too great. People in the late stages have little to lose and are willing to try almost anything. The obvious problem is where to get the donor tissue. Several early studies used tissue from the patients' own adrenal gland. Although that tissue is not composed of neurons, it does produce dopamine. Unfortunately, the adrenal gland transplants seldom produced much benefit (Backlund et al., 1985).

Another possibility is to transplant brain tissue from aborted fetuses. Fetal neurons transplanted into the brain of patients with Parkinson's sometimes survive for years and make synapses with the patients' own cells. However, the operation is expensive and difficult, requiring brain tissue from four to eight fetuses aborted at just the right stage of development. For years, the benefits to the patients were small at best (Freed et al., 2001; Olanow et al., 2003). Results improved when physicians aided survival of the graft by giving drugs to suppress the immune reaction. Occasionally the procedure has been reasonably successful. One 59-year-old man improved dramatically, and for the next 10 years he had only minor symptoms, while remaining on a low dose of L-dopa, before he gradually deteriorated. When he died 24 years after the operation, a postmortem analysis revealed that thousands of the transplanted cells had survived, with intact synapses (Li et al., 2016). So, the procedure can work, but the expense and difficulty make it impractical for the huge number of patients with Parkinson's disease.

A related approach is to take **stem cells**—immature cells that can differentiate into other cell types—and guide their development to produce large quantities of L-dopa before transplanting them into the brain. Getting this procedure to work requires programming the cells to make appropriate connections and suppressing their tendency to form tumors. Methods of doing so have improved, and clinical trials are underway (Parman et al., 2021).

Stop & Check

23. How does L-dopa relieve the symptoms of Parkinson's disease?
24. If neuronal transplants were successful for Parkinson's disease, what would be the advantage over L-dopa?

See page 254 for the answer.

Huntington's Disease

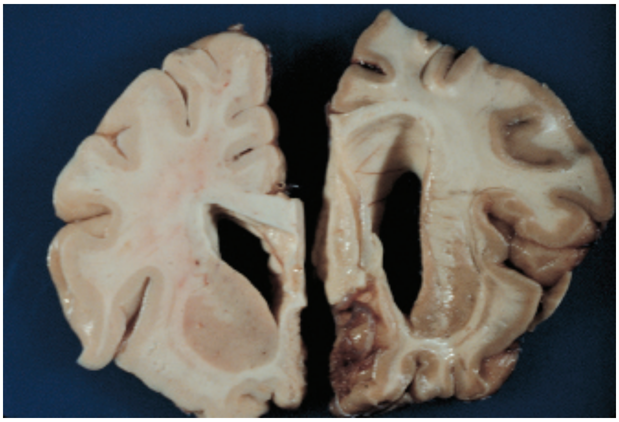
Huntington's disease is a severe neurological disorder that affects about 17 per 100,000 Americans of European ancestry, less than half that many Europeans in Europe itself, probably fewer Africans—although the data for Africa are sparse—and very few Asians (Rawlins et al., 2016).

Motor symptoms usually begin with arm jerks and facial twitches that gradually spread to other parts of the body and develop into writhing. Gradually, the tremors interfere more and more with walking, speech, and other voluntary movements. The disorder is associated with gradual brain damage, especially in the basal ganglia but also in the cerebral cortex (Tabrizi et al., 1999) (Figure 7.21). Because the output from the basal ganglia is inhibitory to the thalamus, damage to the basal ganglia leads to increased activity in parts of the thalamus, producing the involuntary jerky movements.

People with Huntington's disease also suffer psychological disorders including apathy, depression, sleeplessness, memory impairment, anxiety, hallucinations and delusions, poor judgment, alcoholism, drug abuse, and sexual disorders ranging from complete unresponsiveness to indiscriminate promiscuity (Shoulson, 1990). In many cases the psychological problems, especially apathy, become apparent up to 10 years before the motor symptoms lead to a diagnosis (Martinez-Horta et al., 2016).

Figure 7.21 Brain of a normal person (left) and a person with Huntington's disease (right)

The angle of cut through the normal brain makes the lateral ventricle look larger in this photo than it actually is. Even so, note how much larger it is in the patient with Huntington's disease. The ventricles expand because of the loss of neurons.



(**Source:** Robert E. Schmidt, Washington University)

Huntington's disease can have onset at any age, but most often between the ages of 30 and 50. Although the symptoms emerge in adulthood, abnormalities in the nervous system appear early, even during prenatal development (Barnat et al., 2020; Capizzi et al., 2022). Like Parkinson's disease, Huntington's is a progressive disease. Both the psychological and motor symptoms grow progressively worse and culminate in death.

Stop & Check

25. Why does damage to the basal ganglia lead to involuntary movements?

See page 254 for the answer.

Heredity and Presymptomatic Testing

Of all the conditions we consider in this text other than color vision deficiency, Huntington's disease is the only one that can be traced to a single gene. That gene is an autosomal dominant gene (i.e., not on the X or Y chromosome). As a rule, a mutant gene that causes the loss of a function is recessive. The fact that the Huntington's gene is dominant implies that it produces the gain of an undesirable function.

Imagine that as a young adult you learn that your mother or father has Huntington's disease. In addition to your grief about your parent, you know that you have a 50 percent chance of getting the disease yourself. Would you want to know in advance whether or not you were going to get the disease?

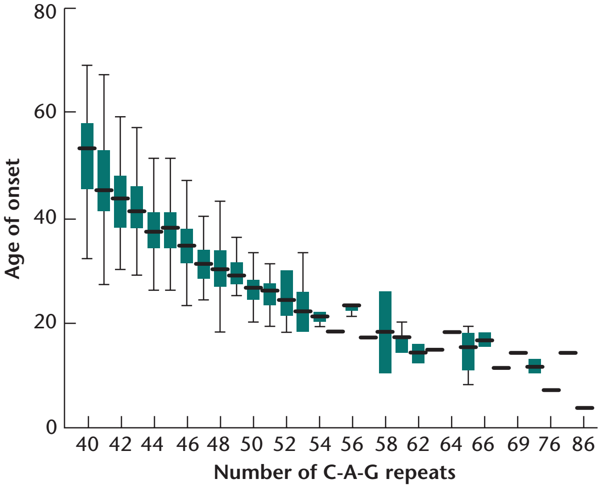
In 1993, researchers located the gene for Huntington's disease on chromosome number 4, a spectacular accomplishment for the technology available at the time (Huntington's Disease Collaborative Research Group, 1993). An examination of your chromosomes can reveal with almost perfect accuracy whether or not you will get Huntington's disease. Knowing the answer might help you decide whether to have children, whether to enter a career that required many years of education, and so forth. However, getting bad news might be depressing. Most people who are at risk choose not to be tested, and about half of those who do get tested do not return to the clinic to learn the results. As is often the case, people try to avoid threatening or unpleasant information (Hertwig and Engel, 2016).

The critical area of the gene is a sequence of bases C-A-G (cytosine, adenine, guanine), repeated 11 to 24 times in most people. That repetition produces a string of 11 to 24 glutamines in the resulting protein. People with up to 35 C-A-G repetitions are considered safe from Huntington's disease. Those with 36 to 38, possibly even 39 or 40 might not get the disease, and if they do, it probably will not manifest until old age (Kay et al., 2016). People with more repetitions are nearly certain to get the disease, unless they die of other causes earlier.

The more C-A-G repetitions someone has, the earlier the probable onset of the disease, as represented in Figure 7.22 (U.S.–Venezuela Collaborative Research Project, 2004). In short, a chromosomal examination predicts not only whether someone will get Huntington's disease but also approximately when the symptoms will emerge. The graph in Figure 7.22 demonstrates considerable

Figure 7.22 Relationship between C-A-G repeats and age of onset of Huntington's disease

For each number of C-A-G repeats, the graph illustrates the age of onset. The green bars indicate the range that includes the middle 50 percent of observations, from the 75th percentile to the 25th percentile. The vertical lines show the full range of observations.



(**Source:** From the U.S.-Venezuela Collaborative Research Project (2004). *Proceedings of the National Academy of Sciences, USA, 101*, pp. 3498–3503.)

variation in age of onset, especially for those with fewer C-A-G repeats. Evidently other factors besides genes also influence the age of onset, such as stressful experiences, drug or alcohol abuse, and perhaps diet and exercise (Byars et al., 2012).

Figure 7.23 presents data for Huntington's disease and seven other neurological disorders. Each of them relates to an extended sequence of C-A-G repeats in a gene. Several other conditions not represented in the figure also relate to an extended sequence of repeats (Boivin et al., 2021; Nelson et al., 2013). For each condition, people with the greatest number of repeats have the earliest onset of symptoms (Gusella and MacDonald, 2000). Those with fewer repeats have not only a later onset but also more variation in age of onset, implying an environmental influence. As a rule, heritability is greater for early-onset disorders than for those with later onset. The same pattern holds for Parkinson's disease, Alzheimer's disease, alcoholism, depression, and schizophrenia.

Identification of the gene for Huntington's disease led to the discovery of the protein that it codes, which has been designated **huntingtin.** Huntingtin occurs throughout the human body, although its mutant form produces no apparent harm outside the brain. The mutant form impairs neurons and glia in several ways, including effects on mitochondria and potassium channels (Tong et al., 2014; Yano et al., 2014). In the early stages of the disease, it increases neurotransmitter release, sometimes causing overstimulation of the target cells (Romero et al., 2008). It also impairs the transport of chemicals down the axon (Morfini et al., 2009).

Identifying the abnormal huntingtin protein and its cellular functions has enabled investigators to search for drugs that might be helpful. Progress has been slow, but medications that reduce the production of the huntingtin protein have exhibited some promise (Leavitt et al., 2020).

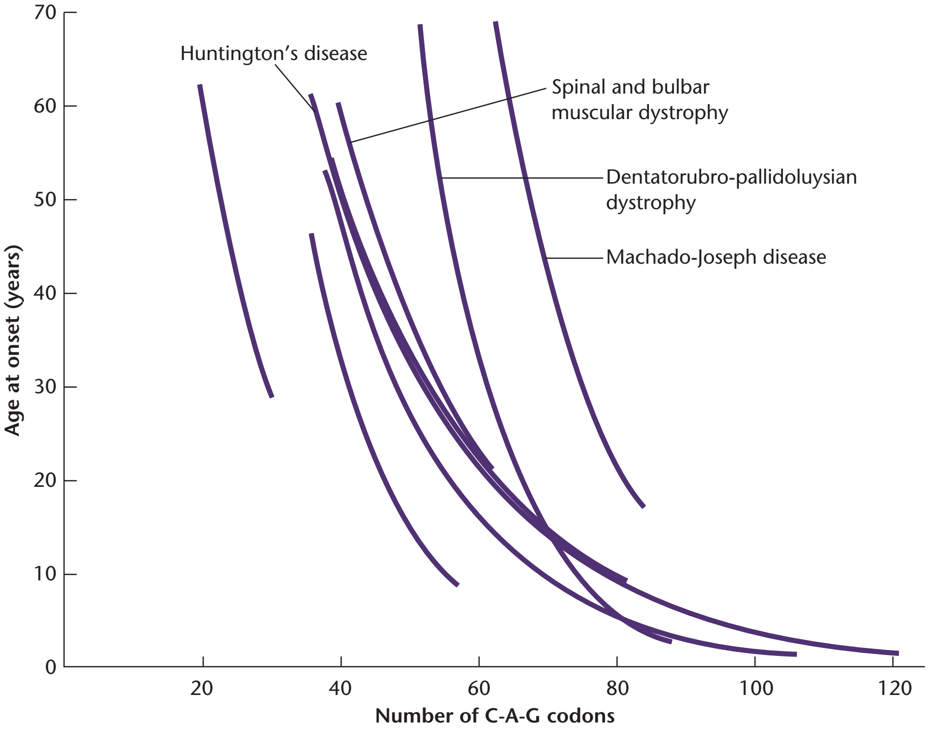
Stop & Check

26. What procedure enables physicians to predict who will or will not get Huntington's disease and to estimate the age of onset?

See page 254 for the answer.

Figure 7.23 Relationship between C-A-G repeats and age of onset of eight diseases

The *x* axis represents the number of C-A-G repeats, and the *y* axis represents the mean age at onset of disease. The unlabeled lines are for four types of spinocerebellar ataxia. For each disease, more repeats causes earlier onset of symptoms.



(**Source:** Reproduced with permission from "Molecular genetics: Unmasking polyglutamine triggers in neurogenerative disease," by J. F. Gusella and M. E. MacDonald, Figure.1, p. 111 in *Neuroscience, 1*, pp. 109–115, copyright 2000 Macmillan Magazines, Ltd.)

Module 7.3 | In Closing

Movement Disorders Affect More than Movement

Parkinson's disease and Huntington's disease emphasize the point that control of movement is closely related to cognition. People with either condition are likely to suffer apathy, cognitive deficits, and a lack of pleasure and motivation. The psychological problems often develop before any noticeable motor problems. In short, the mechanisms of movement are also the mechanisms of thought.

Summary

1. Parkinson's disease and Huntington's disease result from brain deterioration that includes the basal ganglia. **249**
2. Parkinson's disease is characterized by impaired initiation of activity, slow and inaccurate movements, tremor, rigidity, depression, and cognitive deficits. **249**
3. Parkinson's disease is caused by degeneration of dopamine-containing axons from the substantia nigra to the caudate nucleus and putamen. **249**
4. The degeneration of dopamine axons results from both genetic predispositions and environmental toxins. **250**
5. The most common treatment for Parkinson's disease is L-dopa, which crosses the blood–brain barrier and enters neurons that convert it into dopamine. However, replacing dopamine does not halt the underlying deterioration in the brain. Electrical stimulation of the brain is another treatment. **250**
6. Theoretically it may be possible to alleviate Parkinson's disease by implanting stem cells or growth factors, although the results so far have been disappointing. **251**
7. Huntington's disease is a hereditary condition marked by deterioration of motor control as well as apathy, depression, memory impairment, and other cognitive disorders. **251**
8. By examining a gene on chromosome 4, physicians can determine whether someone is likely to develop Huntington's disease. The more C-A-G repeats in the gene, the earlier the likely onset of symptoms. **252**
9. The gene responsible for Huntington's disease alters the structure of a protein. Inhibiting the production of that protein is a theoretically possible treatment. **253**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary.

huntingtin **253**
Huntington's disease **251**
L-dopa **250**
MPP^+ **250**
MPTP **250**
Parkinson's disease **249**
stem cells **251**

Thought Question

Haloperidol is a drug that blocks dopamine synapses. What effect would it probably have for Parkinson's disease?

Stop & Check Answers

21. The striatum organizes and motivates actions, and inhibits unwanted actions. After decrease of input to the striatum in Parkinson's disease, movements are weak and hard to initiate, and unwanted tremors are common.
22. Exposure to harmful chemicals increases the risk. Caffeine, nicotine, and exercise decrease the risk.
23. L-dopa enters the brain, where neurons convert it to dopamine.
24. L-dopa reduces symptoms but does not halt or reverse the progression of the disease. Potentially, neuronal transplants might undo some of the damage.
25. Output from the basal ganglia to the thalamus is inhibitory. After damage to the basal ganglia, the thalamus, and therefore the cortex, receive less inhibition, leading to unwanted actions.
26. Physicians can count the number of consecutive repeats of the combination C-A-G on one gene on chromosome 4.

Module 7.3 | End-of-Module Quiz

1. What is meant by a "progressive" disease?
   - **a.** One that changes into a different disease
   - **b.** One that gets better over time
   - **c.** One that gets worse over time
   - **d.** One that produces benefits as well as harm

2. What causes Parkinson's disease?

- **a.** Loss of dopamine output from the cortex
- **b.** Loss of dopamine input to the striatum
- **c.** Accumulation of amyloid in the brain
- **d.** Excessive activity at acetylcholine synapses

3. Why does decreased activity in the striatum cause Parkinson's disease?

- **a.** The striatum strengthens all reflexive behaviors.
- **b.** The striatum motivates and energizes movement.
- **c.** Axons from the striatum form the medial corticospinal tract.
- **d.** Axons from the striatum form the lateral corticospinal tract.

4. The heritability of Parkinson's disease is highest for which of the following?

- **a.** Females
- **b.** Males
- **c.** Onset in old age
- **d.** Early onset

5. In what way is L-dopa treatment for Parkinson's disease unusual?

- **a.** It produces behavioral benefits without entering the brain.
- **b.** Unlike most drugs, it produces no unpleasant side effects.
- **c.** The treatment becomes more and more effective over time.
- **d.** It was based on a theory instead of trial and error.

6. Which of these is unusual about Huntington's disease?

- **a.** It is caused by a single gene.
- **b.** It is caused by exposure to toxic chemicals in the environment.
- **c.** It is equally common in all parts of the world.
- **d.** It can be treated by increasing dopamine in the brain.

7. Why does damage to the basal ganglia lead to involuntary movements in Huntington's disease?

- **a.** The damage interrupts inhibitory axons from the primary motor cortex to the spinal cord.
- **b.** The cerebellum takes over the functions of the basal ganglia and overcompensates.
- **c.** The person voluntarily tries to overcome the lack of coordination.
- **d.** Basal ganglia damage reduces inhibition of the thalamus.

8. An examination of C-A-G repeats on one gene enables physicians to predict who will develop Huntington's disease. What else does it help them predict?

- **a.** What other diseases the person will get
- **b.** The individual's personality
- **c.** The effectiveness of treatment
- **d.** The age of onset of symptoms

Answers: 1c, 2b, 3b, 4d, 5d, 6a, 7d, 8d.

Suggestions for Further Reading

Klawans, H. L. (1996). *Why Michael couldn't hit.* New York: Freeman. A collection of fascinating sports examples related to the brain and its disorders.

Lashley, K. S. (1951). The problem of serial order in behavior. In L. A. Jeffress (Ed.), *Cerebral mechanisms in behavior* (pp. 112–136). New York: Wiley. This classic article in psychology is a thought-provoking appraisal of what a theory of movement should explain.

For detailed information about brain-machine interfaces to aid movement in people with paralysis, do a YouTube search for Miguel Nicolelis.

Chapter 8

Sleep is an important part of life for nearly all animals.

(Ermolaev Alexander/Shutterstock.com)

Wakefulness and Sleep

Chapter Outline

Module 8.1

Rhythms of Waking and Sleeping
Endogenous Rhythms
Setting and Resetting the Biological Clock
Mechanisms of the Biological Clock
In Closing: Sleep–Wake Cycles

Module 8.2

Stages of Sleep and Brain Mechanisms
Sleep and Other Interruptions of Consciousness
Stages of Sleep
Paradoxical or REM Sleep
Brain Mechanisms of Wakefulness, Arousal, and Sleep
Sleep Disorders
In Closing: Stages of Sleep

Module 8.3

Why Sleep? Why REM? Why Dreams?
Functions of Sleep
Functions of REM Sleep
Biological Perspectives on Dreaming
In Closing: Our Limited Self-Understanding

Learning Objectives

After studying this chapter, you should be able to:

1. Define and describe endogenous rhythms.
2. Explain the mechanisms that set and reset the biological clock.
3. Describe the role of the suprachiasmatic nucleus in controlling sleep and wakefulness.
4. Briefly outline the biochemical basis of the circadian rhythm.
5. List and characterize the stages of sleep.
6. List the main characteristics of REM sleep.
7. Describe the brain mechanisms of sleep and REM.
8. Discuss the consequences of the fact that sleep is controlled locally.
9. Discuss disorders of sleep.
10. Evaluate possible explanations of the functions of sleep.
11. Describe species differences in sleep.
12. Evaluate possible explanations of the functions of REM.
13. Describe possible explanations of dreaming.

Anyone deprived of sleep suffers. But if life evolved on another planet with different conditions, could animals evolve life without a need for sleep? Imagine a planet that doesn't rotate on its axis. Some animals evolve adaptations to live in the light area, others in the dark area, and still others in the twilight zone separating light from dark. There would be no need for any animal to alternate active periods with inactive periods on any fixed schedule and perhaps no need for prolonged inactive periods. If you were the astronaut who discovered these sleepless animals, you might be surprised.

Now imagine that astronauts from that planet set out on their first voyage to Earth. Imagine *their* surprise to discover animals like us with long inactive periods resembling death. To someone who hadn't seen sleep before, it would seem mysterious indeed. For the purposes of this chapter, let's adopt their perspective and ask why we spend a third of our lives doing so little.

Module 8.1

Rhythms of Waking and Sleeping

Learning Objectives

After studying this module, you should be able to:

1. Define and describe endogenous rhythms.
2. Explain the mechanisms that set and reset the biological clock.
3. Describe the role of the suprachiasmatic nucleus in controlling sleep and wakefulness.
4. Briefly outline the biochemical basis of the circadian rhythm.

You are probably not amazed to learn that your body spontaneously generates its own rhythm of wakefulness and sleep. Psychologists of an earlier era strongly resisted that idea. When radical behaviorism dominated experimental psychology during the mid-1900s, many psychologists believed that every behavior was a response to external stimuli. They assumed that alternation between wakefulness and sleep must depend on stimuli from the outside world, including changes in light or temperature. Research as early as that of Curt Richter (1922) implied that the body generates its own cycles of activity and inactivity, but it took decades of research to convince the skeptics. The idea of self-generated rhythms was a major step toward viewing animals as active producers of behaviors.

Endogenous Rhythms

An animal that produced its behavior entirely in response to current stimuli would be at a serious disadvantage. Animals need to anticipate changes in the environment. For example, migratory birds start flying toward their winter homes before their summer territory becomes too cold. A small bird that waited for the first frost would be in serious trouble. Similarly, squirrels begin storing nuts and putting on extra layers of fat in preparation for winter long before food becomes scarce.

Changes in the light–dark pattern of the day tell a migratory bird when to fly south for the winter, but how does it know when to fly back north? In the tropics, the temperature and amount of daylight are nearly the same throughout the year. Nevertheless, migratory birds fly north at the right time. Even if they are kept in a cage with no clues to the season, they become restless in the spring, and if they are released, they fly north (Gwinner, 1986). In some way their brain is keeping track of the date to generate an **endogenous circannual rhythm**. (*Endogenous* means "generated from within." *Circannual* comes from the Latin words *circum*, for "about," and *annum*, for "year.")

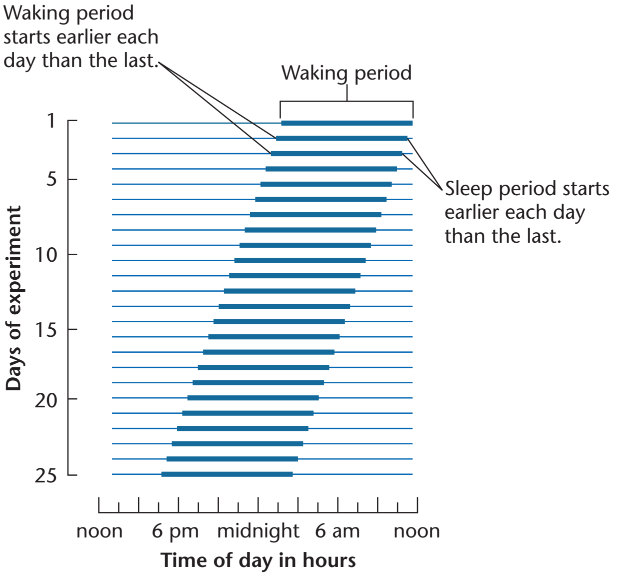
Animals also produce **endogenous circadian rhythms** that last about a day. (*Circadian* comes from the Latin *circum*, for "about," and *dies*, for "day.") If you go without sleep all night—as most college students do, sooner or later—you feel sleepier and sleepier as the night goes on, but when morning arrives, you feel more alert, not less. Especially in the posterior areas of the cerebral cortex, activity correlates mainly with your circadian rhythm, and only secondarily with how long you have been awake (Muto et al., 2016).

Figure 8.1 represents the activity of a flying squirrel kept in total darkness for 25 days. Each horizontal line represents one 24-hour day. A thickening in the line represents a period of activity. Even in this unchanging environment, the animal generates a consistent rhythm of activity and sleep. Depending on the individual and the details of the procedure, the self-generated cycle may be slightly shorter than 24 hours, as in Figure 8.1, or slightly longer (Carpenter and Grossberg, 1984).

Humans also generate 24-hour wake–sleep rhythms, which we can modify only a little. If we ever send astronauts to Mars, they will have to adjust to the Martian day, which lasts about 24 hours and 39 minutes of Earth time. Engineers who were monitoring the Phoenix robot mission on Mars had to live on the Martian schedule, starting work 39 minutes later each day. Most (13 of the 15 who were studied) managed to synchronize their biological rhythms to the Martian schedule, although they did not sleep as much as usual, and some of them suffered a loss of alertness (Barger et al., 2012).

Figure 8.1 Activity record of a flying squirrel kept in constant darkness

The thickened segments indicate periods of activity as measured by a running wheel. Note that this free-running activity cycle lasts slightly less than 24 hours.



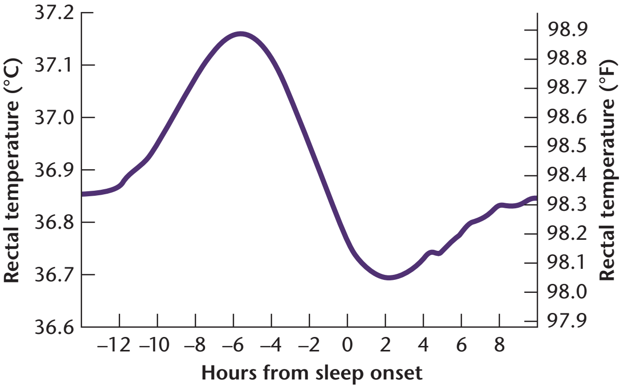
(**Source:** From "Phase control of activity in a rodent," by P. J. DeCoursey, 1960, *Cold Spring Harbor Symposia on Quantitative Biology, 25*, pp. 49–55. Reprinted by permission of Cold Spring Harbor and P. J. DeCoursey.)

Our circadian rhythm does not easily adjust to more severe departures from a 24-hour schedule. Naval personnel on submarines are cut off from sunlight for months at a time, living under artificial light. In some cases, they live on a schedule of 6 hours of work, 6 hours of recreation, and 6 hours of sleep. Although they try to sleep on this 18-hour schedule, their bodies generate rhythms of alertness and body chemistry that continue to average a bit more than 24 hours, and their alertness suffers (Kelly et al., 1999).

Circadian rhythms affect more than just waking and sleeping. We have circadian rhythms in our hunger, thirst, liver activity, insulin secretion, intestinal activity, DNA repair, and much else (Bass and Lazar, 2016). Although we ordinarily think of human body temperature as 37° C, our temperature fluctuates over the course of a day from a low near 36.7° C during the night to almost 37.2° C in late afternoon (Figure 8.2). We also have circadian rhythms in mood. In one study, young adults recorded their mood throughout the day. Most showed increases in positive mood (happiness) from waking until late afternoon, and then a slight decline until bedtime. In a follow-up study, the same investigators kept young adults awake for 30 consecutive hours, starting at either 10 A.M. or 5 P.M., in a setting with constant levels of light and temperature. Regardless of whether people started this procedure at 10 A.M. or 5 P.M., most reported their most pleasant mood around 5 P.M. and their least pleasant mood at around 5 A.M. (Murray et al., 2009). These results suggest a biologically driven circadian rhythm in emotional well-being (Figure 8.3).

Figure 8.2 Mean rectal temperatures for nine adults

Body temperature reaches its low for the day about 2 hours after sleep onset; it reaches its peak about 6 hours before sleep onset.



(**Source:** From "Sleep-onset insomniacs have delayed temperature rhythms," by M. Morris, L. Lack, and D. Dawson, 1990, *Sleep, 13*, pp. 1–14. Reprinted by permission.)

Stop & Check

1. What evidence indicates that humans have an internal biological clock?

See page 267 for the answer.

Setting and Resetting the Biological Clock

Your circadian rhythm is close to 24 hours, but it is not perfect. Unless something resets your circadian rhythm, it would gradually drift away from the correct time. The stimulus that resets your circadian rhythm is referred to by the German term **zeitgeber** (TSITE-gay-ber), meaning "time-giver." Light is by far the dominant zeitgeber for land animals (Rusak and Zucker, 1979), whereas the tides are important for some marine animals. In addition to light, other zeitgebers include exercise (Eastman et al., 1995), arousal (Gritton et al., 2009), meals, and the temperature of the environment (Refinetti, 2000). Social stimuli—that is, the effects of other people—are ineffective as zeitgebers, unless they induce exercise or other vigorous activity (Mistlberger and Skene, 2004). Although these additional zeitgebers modify the effects of light, they have only weak effects. People who are working in Antarctica during the constant darkness of an Antarctic winter maintain an approximately 24-hour rhythm, but different people generate

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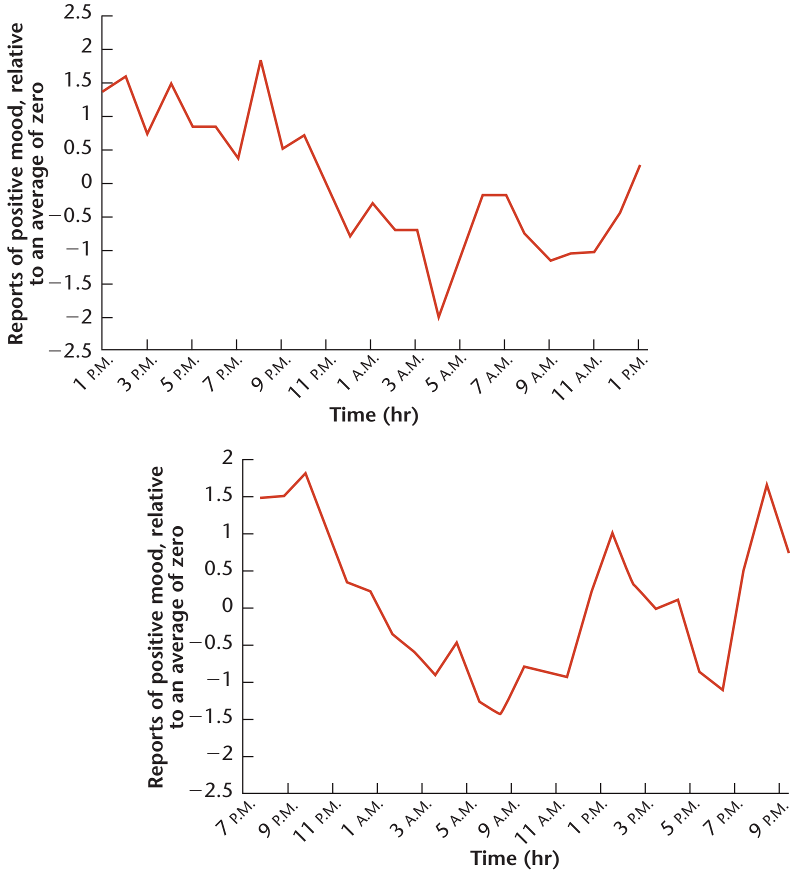
Figure 8.3 Reported positive mood over time

During 30 hours in an unchanging laboratory environment, the average young adult reported most pleasant mood in the late afternoon or early evening, and the least pleasant mood around 5 to 7 A.M. The pattern was similar for those who started the procedure in the morning (above) or in the evening (below).



(**Source:** From "Nature's clocks and human mood: The circadian system modulates reward motivation," by G. Murray et al., 2009, *Emotion, 9*, pp. 705–716.)

slightly different rhythms, until they find it more and more difficult to work together (Kennaway and Van Dorp, 1991). Astronauts in orbit face a special problem: As they orbit the Earth, a 45-minute period of daylight alternates with 45 minutes of darkness. If they retreat from the flight deck to elsewhere in the spacecraft, they have constant dim light. As a result, they are not fully alert during their wakeful periods or deeply asleep during rest periods (Dijk et al., 2001). On long assignments, many of them experience depression and impaired performance (Mallis and DeRoshia, 2005).

When we try to set our wake–sleep cycles by the clock, sunlight still has its influence. Consider what happens when we shift to daylight saving time in spring. You set your clock to an hour later, and when it shows your usual bedtime, you dutifully go to bed, even though it seems an hour too early. The next morning, when the clock says it is 7 A.M. and time to get ready for work, your brain registers 6 A.M. Most people remain ill rested for days after the shift to daylight saving time. The adjustment is especially difficult for people who were already sleep deprived, including most college students (Lahti et al., 2006; Monk and Aplin, 1980). In fall, when daylight saving time ends, some people have sleep problems then, too (Harrison, 2013).

A similar problem can happen on a weekend, when you might be freer to set your own schedule. If you stay up late on Friday and Saturday nights, exposed to noises and bright lights, and awaken late the next mornings, then on Monday morning your biological clock may say 5 A.M. when it is actually 7 A.M., and you stagger off to work or school without much pep (Moore-Ede et al., 1983).

Particularly impressive evidence for the importance of sunlight comes from a study in Germany. Sunrise occurs at the eastern end of Germany about half an hour earlier than at the western end, but all people set their clocks to the same time. Researchers asked adults for their preferred times of awakening and going to sleep and determined for each person the midpoint of those values. For example, if on weekends and holidays you prefer to go to bed at 12:30 A.M. and awaken at 8:30 A.M., your sleep midpoint is 4:30 A.M. Figure 8.4 illustrates the results.

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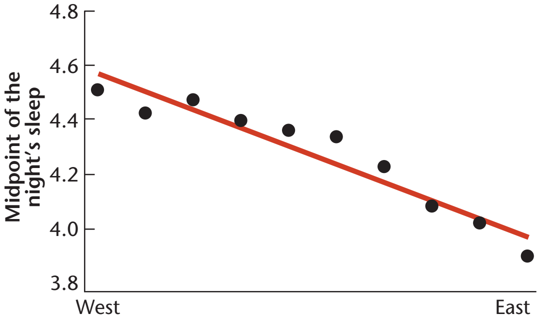
Figure 8.4 Sun time competes with social time

When people have no obligation to awaken at a particular time, they awaken about half an hour earlier at the eastern edge of Germany than at the western edge. Points along the *y* axis represent the midpoint between the preferred bedtime and the preferred waking time. Data are for people living in towns and cities with populations less than 300,000.



(**Source:** From "The human circadian clock entrains to sun time," by T. Roenneberg, C. J. Kumar, and M. Merrow, 2007, *Current Biology, 17*, pp. R44–R45. Reprinted by permission of the Copyright Clearance Center.)

People at the eastern edge have a sleep midpoint about 30 minutes earlier than those at the west, corresponding to the fact that the sun rises earlier at the eastern edge (Roenneberg et al., 2007). Other researchers reported similar results for Turkey and South Africa (Masal et al., 2015; Shawa and Roden, 2016).

What about blind people, who need to set their circadian rhythms by zeitgebers other than light? The results vary. Some do set their circadian rhythms by noise, temperature, meals, and activity. However, those who are not as sensitive to these secondary zeitgebers produce circadian rhythms that are a little longer than 24 hours. When their cycles are in phase with the clock, all is well, but when they drift out of phase, they may experience insomnia at night and sleepiness during the day (Sack and Lewy, 2001). Most blind people report frequent sleep problems (Warman et al., 2011).

Stop & Check

2. Why do people at the eastern edge of a time zone awaken earlier than those at the western edge on their weekends and holidays?

See page 267 for the answer.

Jet Lag

A disruption of circadian rhythms after crossing time zones is known as **jet lag**. Travelers complain of sleepiness during the day, sleeplessness at night, and sometimes depression and impaired concentration (Haimov and Arendt, 1999). Most people find it easier to adjust to crossing time zones going west than east. Going west, we stay awake later at night and then awaken late the next morning, already partly adjusted to the new schedule. We *phase-delay* our circadian rhythms. Going east, we *phase-advance* to sleep earlier and awaken earlier (Figure 8.5). Most people find it difficult to go to sleep before their body's usual time and difficult to wake up early the next day.

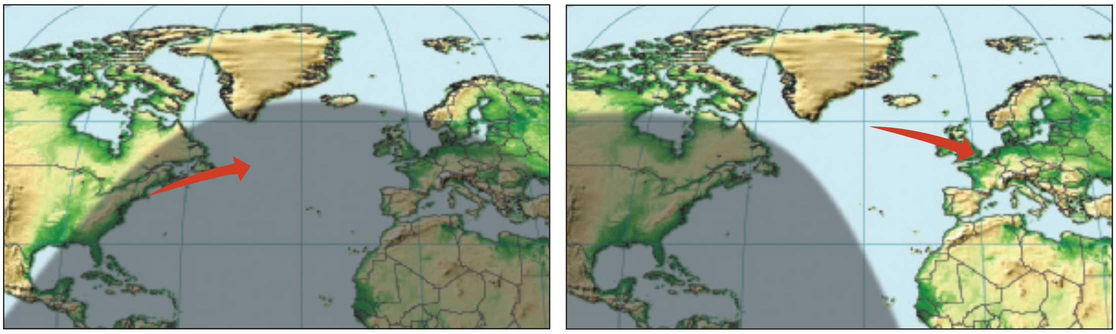
Adjusting to jet lag is stressful. Stress elevates blood levels of the adrenal hormone *cortisol*, and prolonged elevation of cortisol damages neurons in the hippocampus, an area important for memory. One study examined flight attendants who had spent the previous 5 years making flights across seven or more time zones—such as Chicago to Italy—usually having breaks of fewer than 6 days between trips. On the average, the flight attendants had smaller than average volumes of the hippocampus and surrounding structures, and they showed memory impairments (Cho, 2001). These results suggest a danger from repeated adjustments of the circadian rhythm, although the problem here could be air travel itself. A good control group would have been flight attendants who flew long north–south routes.

Night Work

People who work on a night shift, such as midnight to 8 A.M., sleep during the day. At least they try to. Even after

Figure 8.5 Jet lag

Eastern time is later than western time. People who travel six time zones east fall asleep on the plane and then must awaken when it is morning at their destination but night back home.



(a) Leave New York at 7 P.M. (b) Arrive in London at 7 A.M., which is 2 A.M. in New York

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months or years on such a schedule, many workers continue to feel groggy on the job, they sleep poorly during the day, and their body temperature continues to peak when they are sleeping in the day instead of while they are working at night. On average, night-shift workers have more accidents than day-shift workers.

It is difficult to adjust the circadian rhythm to work at night, because most buildings use artificial lighting in the range of 150 to 180 lux, which is only moderately effective in resetting the rhythm (Boivin et al., 1996). People adjust better if they sleep in a very dark room during the day and work under very bright lights at night, comparable to the noonday sun (Czeisler et al., 1990). Short-wavelength (bluish) light resets the circadian rhythm more strongly than long-wavelength light does (Czeisler, 2013).

Morning People and Evening People

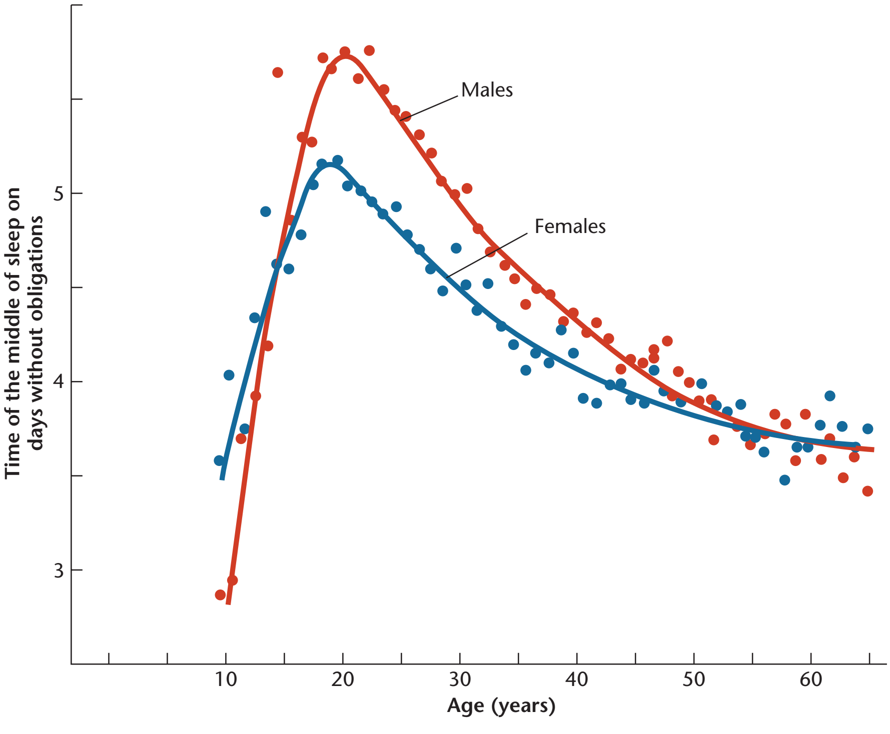
Circadian rhythms differ among individuals. Some people ("morning people" or "larks") awaken early, reach their peak of productivity early, and become less alert later. Others ("evening people" or "owls") warm up slowly, both literally and figuratively, reaching their peak in the late afternoon or evening. They tolerate staying up all night better than morning people do (Taillard et al., 2003). Among shift workers, morning people are most impaired when working the night shift and evening people are most impaired when working the morning shift (Juda et al., 2013). Many people are intermediate between the two extremes.

A convenient way to classify people is to ask, "On holidays and vacations when you have no obligations, what time is the middle of your sleep?" For example, if you sleep from 1 A.M. until 9 A.M. on those days, your middle is 5 A.M. As Figure 8.6 illustrates, people differ by age. As children, many of us went to bed early and woke up early. As we entered adolescence, we more likely preferred staying up later and waking up later. The mean preferred time of going to sleep gets later until about age 20 and then gradually reverses (Roenneberg et al., 2004). The tendency to stay up later during adolescence occurs in every culture that researchers have studied throughout the world (Gradisar et al., 2011). The same trend also occurs in rats, monkeys, and other species (Hagenauer and Lee, 2012; Winocur and Hasher, 1999, 2004), apparently triggered by increased levels of sex hormones (Hagenauer and Lee, 2012; Randler et al., 2012). From a functional standpoint, we can only speculate as to why staying up late and waking up late might be more advantageous for adolescents than for children or adults.

So, being a "morning person" or an "evening person" depends partly on age. It also depends on genetics and several

Figure 8.6 Age differences in circadian rhythms

People reported the time of the middle of their sleep, such as 3 A.M. or 5 A.M., on days when they had no obligations.



(**Source:** Reprinted from "A marker for the end of adolescence," by T. Roenneberg et al., *Current Biology, 14*, pp. R1038–R1039, Figure 1, copyright 2004, with permission from Elsevier.)

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environmental factors. In low-tech societies without electric lights, people go to sleep about three hours after sunset, seldom awaken during the night, and wake up at sunrise. After a society gains electric lights, people stay awake later and get less sleep (de la Iglesia et al., 2015; Yetish et al., 2015). People who live in a big city, surrounded by bright lights, are more likely to stay up late than are people in rural areas.

The tendency for most young people to be evening types causes problems. In the United States and many other countries, high school classes start at 8:00 A.M. or earlier, while most teenagers are at least a bit drowsy at that time. Those who are strongly evening types tend to get lower than average test scores, especially in their morning classes (Preckel et al., 2011; Preckel et al., 2013; van der Vinne et al., 2015). As an experiment, 753 Argentinian high school students were randomly assigned to start school at 7:45 A.M., 12:40 P.M., or 5:20 P.M. For those starting at 7:45, the morning types did substantially better in all courses. At later times, the advantage was reduced or slightly reversed (Goldin et al., 2020). In both adolescence and adulthood, morning people report being happier than evening people, on average, at least partly because their biological rhythms are more in tune with their school or work schedule (Biss and Hasher, 2012).

Stop & Check

3. From a biological standpoint, why would it be best to start high school classes later in the morning?

See page 267 for the answer.

Mechanisms of the Biological Clock

How does the body generate a circadian rhythm? Curt Richter (1967) first demonstrated that the brain generates its own rhythms—a biological clock—and he found that the biological clock is insensitive to most forms of interference. Blind or deaf animals generate circadian rhythms, although they slowly drift out of phase with the external world. The circadian rhythm remains surprisingly steady despite food or water deprivation, X-rays, tranquilizers, alcohol, anesthesia, lack of oxygen, most kinds of brain damage, or the removal of endocrine organs. Even an hour or more of induced hibernation often fails to reset the biological clock (Gibbs, 1983; Richter, 1975). Evidently, the biological clock is a hardy, robust mechanism.

The Suprachiasmatic Nucleus (SCN)

Although cells throughout the body generate circadian rhythms, the main driver of rhythms for sleep and body temperature is the **suprachiasmatic** (soo-pruh-kie-as-MAT-ik) **nucleus**, or **SCN**, a part of the hypothalamus (Refinetti and Menaker, 1992). It gets its name from its location just above ("supra") the optic chiasm (Figure 8.7). After damage to the SCN, the body's rhythms become erratic.

The SCN generates circadian rhythms automatically. If SCN neurons are disconnected from the rest of the brain or removed from the body and maintained in tissue culture, they continue to produce a circadian rhythm of action potentials (Earnest et al., 1999; Inouye and Kawamura, 1979). A single SCN cell can maintain a circadian rhythm, but not very accurately. Interactions among neurons and astrocytes sharpen the accuracy of the rhythm (Hastings et al., 2018; Long et al., 2005; Yamaguchi et al., 2003).

A mutation in one gene causes hamsters' SCN to produce a 20-hour instead of 24-hour rhythm (Ralph and Menaker, 1988). Researchers surgically removed the SCN from adult hamsters and transplanted SCN tissue from hamster fetuses into the adults. When they transplanted SCN tissue from fetuses with a 20-hour rhythm, the recipients produced a 20-hour rhythm. When they transplanted tissue from fetuses with a 24-hour rhythm, the recipients produced a 24-hour rhythm (Ralph et al., 1990). That is, the rhythm followed the pace of the donors, not the recipients. In short, the rhythms come from the SCN itself.

Stop & Check

4. What evidence strongly indicates that the SCN produces the circadian rhythm itself?

See page 267 for the answer.

How Light Resets the SCN

Figure 8.7 illustrates the position of the SCN in the human brain, just above the optic chiasm. A small branch of the optic nerve, the *retinohypothalamic path* from

Elliott Blass/University of Massachusetts at Amherst

Curt P. Richter (1894–1988)

I enjoy research more than eating. (Richter, personal communication)

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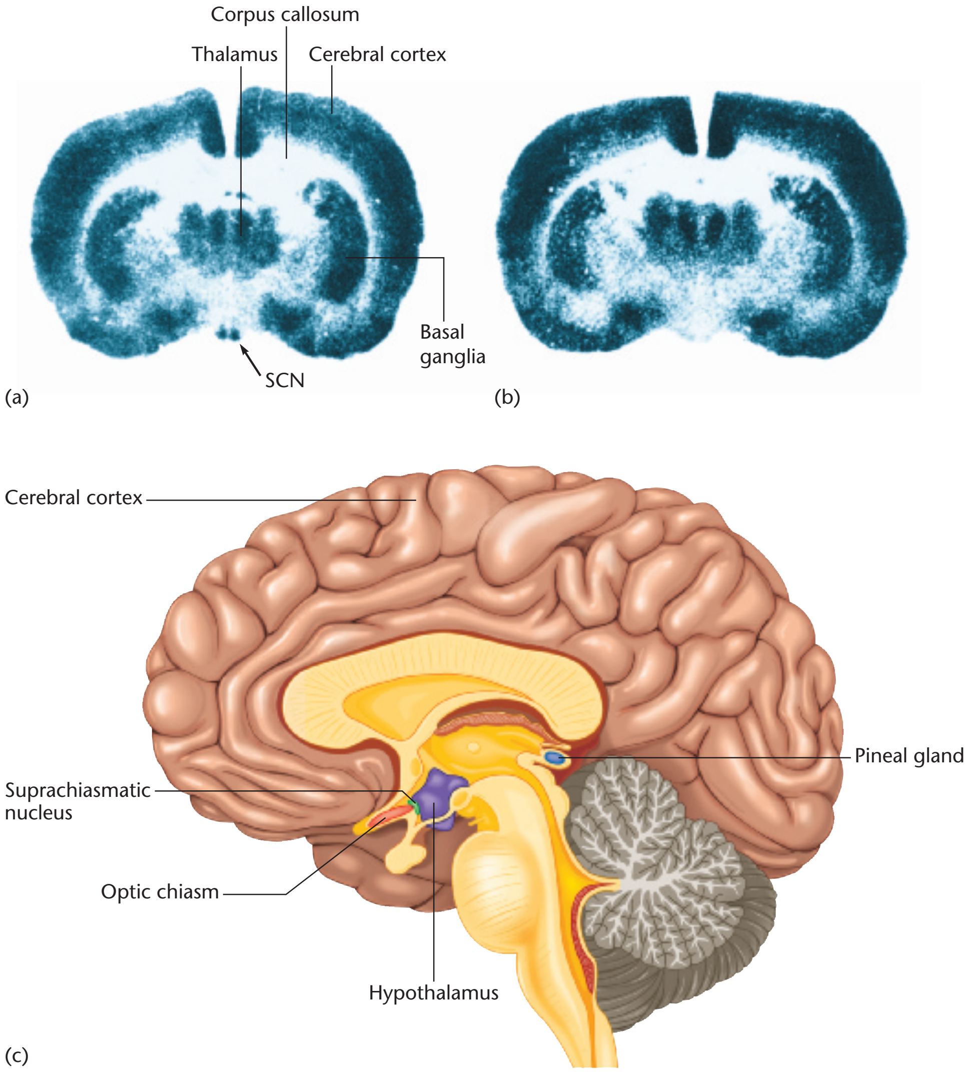
Figure 8.7 The suprachiasmatic nucleus (SCN) of rats and humans

The SCN is at the base of the brain, as illustrated in these coronal sections through the plane of the anterior hypothalamus. A darker appearance indicates greater activity by neurons, causing them to absorb more of the radioactive marker used in this study. Below: A sagittal section through a human brain depicting the location of the SCN and the pineal gland.



(**Source:** From "Suprachiasmatic nucleus: Use of 14C-labeled deoxyglucose uptake as a functional marker," by W. J. Schwartz and H. Gainer, 1977, *Science, 197*, pp. 1089–1091. Reprinted by permission from AAAS/American Association for the Advancement of Science.)

the retina to the SCN, alters the SCN's settings. Most of the input to that path does not come from normal retinal receptors. Mice with genetic defects that destroy nearly all their rods and cones nevertheless respond to light by resetting their biological clocks (Freedman et al., 1999; Lucas et al., 1999). Also, consider blind mole rats (Figure 8.8), whose eyes are covered with folds of skin and fur. They are evolutionarily adapted to spend most of their lives underground. They have fewer than 900 optic nerve axons, compared with 100,000 in hamsters. Even a bright flash of light evokes no startle response and no measurable change in brain activity. Nevertheless, light resets their circadian rhythms, enabling them to be awake only at night (de Jong et al., 1990).

The explanation is that the retinohypothalamic path to the SCN comes from certain retinal ganglion cells that have their own photopigment, *melanopsin* (Hannibal et al., 2001; Lucas et al., 2001). These special ganglion cells receive some input from rods and cones (Gooley et al., 2010; Güler et al., 2008), but even without that input, they respond directly to light (Berson et al., 2002). They are located mainly near the nose, and therefore they see toward

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Figure 8.8 A blind mole rat

Although blind mole rats are blind in other regards, they reset their circadian rhythms in response to light.

EvgenS/Shutterstock.com

the periphery (Visser et al., 1999). Because they respond slowly when light comes on and decline slowly when the light ceases, they respond to the overall average amount of light, not to instantaneous changes in light (Berson et al., 2002). The average intensity is exactly the information the SCN needs to gauge the time of day. A flash of lightning in the middle of the night does not mean that daytime has arrived.

These ganglion cells respond mainly to short-wavelength (blue) light. Because television, video games, computers, and eReaders emit mostly short-wavelength light, late-evening exposure to them phase-delays the circadian rhythm, makes it difficult to fall asleep, and impairs alertness the next morning (Chang et al., 2015). Wearing glasses that filter out blue light might help.

Stop & Check

5. How does light reset the biological clock?
6. People who are blind because of cortical damage can still synchronize their circadian rhythm to the local pattern of day and night. Why?

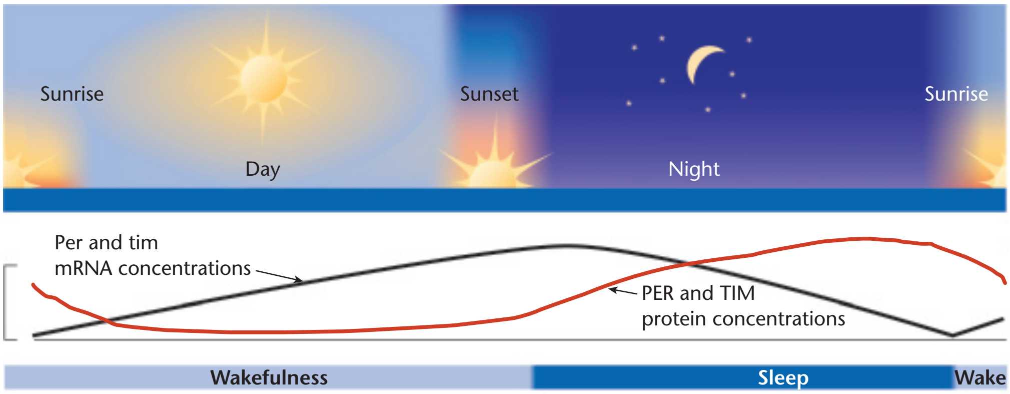
See page 267 for the answer.

Biochemistry of the Circadian Rhythm

Research on production of the circadian rhythm began when studies on the fruit fly *Drosophila* found genes that produce a circadian rhythm (X. Liu et al., 1992; Sehgal et al., 1999). Two of these genes, known as *period* (abbreviated *PER*) and *timeless* (*TIM*), produce the proteins PER and TIM. The concentration of these proteins, which promote sleep, oscillates over a day, based on feedback interactions. Early in the morning, the messenger RNA levels responsible for producing PER and TIM start at low concentrations. As they increase during the day, they slowly increase synthesis of the proteins (Figure 8.9). As the PER and TIM protein concentrations increase, they feed back to inhibit the genes that produce the RNA molecules. During the night, the PER and TIM concentrations remain high, promoting sleep, but the messenger RNA concentrations are declining (Nitabach and Taghert, 2008). By the next morning, PER and TIM protein levels have declined, the fly awakens, and the cycle is ready to start again. Because the feedback cycle takes about 24 hours, a fly can generate a circadian rhythm even in an unchanging environment. However, in addition to the automatic feedback, light activates a chemical that breaks down the TIM protein about as fast as it forms during the day (as represented in the figure), keeping the fly awake. Doing so synchronizes the internal clock to the external world (Ashmore and Sehgal, 2003).

Figure 8.9 Feedback between proteins and genes to control sleepiness

In fruit flies (*Drosophila*), the concentrations of the mRNA levels for PER and TIM oscillate over a day, and so do the proteins that they produce.



Why do we care about flies? The reason is that analyzing the mechanism in flies told researchers what to look for in humans and other mammals. Mammals have several variants of the PER and other proteins found in flies (Reick et al., 2001; Zheng et al., 1999). People with certain PER mutations have a circadian rhythm shorter than 24 hours, as if they were moving about a time zone east every day (Chong et al., 2012; Jones et al., 1999; Zhang et al., 2016). They consistently get sleepy early in the evening and awaken early in the morning. Most people look forward to days when they can stay up late. People with an altered PER gene look forward to times when they can go to bed early. Other genetic mutations can cause the reverse condition, a circadian rhythm longer than 24 hours, marked by difficulty waking up on time in the morning (Gentry et al., 2021). Some of those people might adjust well to the Martian day.

Stop & Check

7. How do the proteins TIM and PER relate to sleepiness in *Drosophila*?

See page 267 for the answer.

Melatonin

The suprachiasmatic nucleus regulates waking and sleeping by controlling activity levels in other brain areas, including the **pineal gland** (PIN-ee-al; Figure 8.7), an endocrine gland located just posterior to the thalamus (Aston-Jones et al., 2001; von Gall et al., 2002). The pineal gland releases the hormone **melatonin**. Melatonin is a widespread chemical, found in nearly all animals—sponges are the only known exception—as well as in plants and bacteria. For all animals, it is released mostly at night. In diurnal animals like humans, it increases sleepiness. People who have pineal gland tumors sometimes stay awake for days at a time (Haimov and Lavie, 1996). In addition to regulating sleep and wakefulness, melatonin also helps control the onset of puberty and adjustments to changes of season, such as hibernation.

Melatonin secretion starts to increase about 2 or 3 hours before bedtime. Taking a melatonin pill in the evening has little effect on sleepiness because the pineal gland produces melatonin at that time anyway. Taking melatonin earlier can hasten the onset of sleepiness and shift the circadian rhythm (Crowley and Eastman, 2013). Melatonin pills are sometimes helpful when people travel across time zones and need to sleep at an unaccustomed time.

Module 8.1 | In Closing

Sleep–Wake Cycles

Unlike an electric appliance that stays on until someone turns it off, the brain periodically turns itself on and off. Our biological mechanisms prepare us to wake at certain times and sleep at other times, even if we would prefer other schedules.

Summary

1. Animals, including humans, have circadian rhythms—internally generated rhythms of activity and sleep lasting about 24 hours. It is difficult to adjust to a sleep schedule much different from 24 hours. **258**
2. Even when people set their waking and sleeping times by the clock, the timing of sunrise influences their circadian rhythm. **259**
3. It is easier for most people to follow a cycle slightly longer than 24 hours (as when traveling west) than to follow a cycle shorter than 24 hours (as when traveling east). **261**
4. If people wish to work at night and sleep during the day, the best way to shift the circadian rhythm is to have bright lights at night and darkness during the day. **261**
5. Some people are most alert early in the morning, and others become more alert later in the day. On average, young adults demonstrate the greatest preference for staying awake late and sleeping late the next morning. **262**
6. The suprachiasmatic nucleus (SCN) of the hypothalamus generates the body's circadian rhythms for sleep and temperature. **263**
7. Light resets the biological clock by a branch of the optic nerve that extends to the SCN. Those axons originate from a special population of ganglion cells that respond directly to light in addition to receiving some input from rods and cones. **263**
8. The genes controlling the circadian rhythm are almost the same in mammals as in insects. Circadian rhythms

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result from genes that produce proteins that feed back to inhibit the genes that produce them. **265**

9. Some people have genetic variations causing their circadian rhythms to run slightly faster or slower than average, affecting their sleep schedule. **266**
10. The suprachiasmatic nucleus controls the body's rhythm partly by directing the release of melatonin by the pineal gland. The hormone melatonin increases sleepiness. If given at certain times of the day, it can also reset the circadian rhythm. **266**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

endogenous circadian rhythms	**258**
endogenous circannual rhythm	**258**
jet lag	**261**
melatonin	**266**
pineal gland	**266**
suprachiasmatic nucleus (SCN)	**263**
zeitgeber	**259**

Thought Question

Why would evolution have enabled blind mole rats to synchronize their SCN activity to light, even though they cannot see well enough to make any use of the light?

Stop & Check Answers

1. People who live in an environment with a light–dark schedule much different from 24 hours fail to follow that schedule and instead become wakeful and sleepy on a 24-hour basis.
2. The sun rises earlier at the eastern edge than at the western edge. Evidently, the sun influences waking–sleeping schedules, even when people follow the clock time for their work schedule.
3. Most young people are evening types, and they reach their peak of alertness later in the day.
4. SCN cells produce a circadian rhythm of activity even if they are kept in cell culture isolated from the rest of the body. Also, when hamsters received transplanted SCN neurons, their circadian rhythm followed the pattern of the donor animals.
5. A branch of the optic nerve, the retinohypothalamic path, conveys information about light to the SCN. The axons comprising that path originate from special ganglion cells that respond to light by themselves, even if they do not receive input from rods or cones.
6. If the retina is intact, melanopsin-containing ganglion cells can still send messages to the SCN, resetting its rhythm.
7. The proteins TIM and PER remain low during most of the day and increase toward evening. They reach high levels at night, promoting sleep. They feed back to inhibit the genes that produce them, so that their level declines toward morning.

Module 8.1 | End-of-Module Quiz

1. How do migratory birds know when to fly north for the spring?
   - **a.** They respond to changes in temperature.
   - **b.** They respond to changes in daylight.
   - **c.** They have an endogenous circannual rhythm.
   - **d.** They follow their food sources as they move north.

2. Workers on certain submarines work 6 hours, relax 6 hours, and then sleep 6 hours. After weeks on this schedule, what happens to their circadian rhythm?
   - **a.** It adjusts to produce an 18-hour rhythm.
   - **b.** It continues producing the usual 24-hour rhythm.
   - **c.** It produces a rhythm intermediate between 18 and 24 hours.
   - **d.** It stops producing any rhythm at all.

3. Why do people working in Antarctica during the winter often find it difficult to work together?
   - **a.** Their work schedules keep them so busy that they cannot sleep enough.
   - **b.** Their circadian rhythms drift out of phase with one another.
   - **c.** After living together in close quarters for so long, they start to irritate one another.
   - **d.** They get homesick.

4. For most young adults, what happens to mood as a function of time of day?
   - **a.** Mood tends to be most pleasant early in the morning.
   - **b.** Mood tends to be most pleasant in the middle of the night.
   - **c.** Mood tends to be most pleasant in late afternoon or early evening.
   - **d.** Mood fluctuates, but on average is about the same for one time as for another.

5. Which of these is evidence that sunlight resets humans' circadian rhythm?

- **a.** Workers on submarines continue producing a circadian rhythm.
- **b.** Mood tends to fluctuate over the course of the day.
- **c.** Teenagers tend to go to sleep later and awaken later than older people.
- **d.** People tend to awaken earlier in eastern Germany than in western Germany.

6. Why do many high school students perform worse in the morning than in the afternoon?

- **a.** Most schools schedule the math and science courses mainly in the morning.
- **b.** Teenagers tend to stay up late and awaken late.
- **c.** Many teenagers do not eat a healthy breakfast.
- **d.** Many high schools are not adequately heated during the morning.

7. Why do many blind people periodically experience something similar to jet lag?

- **a.** They often suffer difficulties and anxieties related to travel.
- **b.** Their suprachiasmatic nucleus deteriorates from lack of input.
- **c.** Their sleep is more likely than average to be disturbed by any noise.
- **d.** Their circadian rhythms drift out of phase with the clock.

8. What evidence most strongly indicates that the SCN produces the circadian rhythm itself?

- **a.** Damage to the SCN disrupts the circadian rhythm.
- **b.** SCN cells isolated from the body continue to produce a circadian rhythm.
- **c.** Animals with a faster circadian rhythm have a larger SCN.
- **d.** The SCN increases its activity during wakeful periods and decreases it during sleep.

9. Light can reset the SCN's rhythm even after damage to all rods and cones. Why?

- **a.** The SCN itself responds to light.
- **b.** The SCN receives input from the pineal gland.
- **c.** The SCN receives input from skin cells that respond to light.
- **d.** The SCN receives input from ganglion cells that respond to light.

10. If you want to get to sleep on time, what should you avoid?

- **a.** Long-wavelength light late in the evening
- **b.** Short-wavelength light late in the evening
- **c.** Long-wavelength light early in the morning
- **d.** Short-wavelength light early in the morning

11. After the proteins TIM and PER reach a high level during the day, what causes their level to decrease at night?

- **a.** High levels of the proteins inhibit the genes that produce these proteins.
- **b.** The genes that produce these proteins become less active when temperature drops.
- **c.** Rapid production of the proteins depleted the supply of the amino acids needed to make them.
- **d.** Decreased light decreases excitatory transmission throughout the nervous system.

12. Which of these does melatonin increase?

- **a.** Sexual arousal
- **b.** Muscle strength
- **c.** Sleepiness
- **d.** Attention

Answers: 1c, 2b, 3b, 4c, 5d, 6b, 7d, 8b, 9d, 10b, 11a, 12c.

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Module 8.2

Stages of Sleep and Brain Mechanisms

Learning Objectives

After studying this module, you should be able to:

5. List and characterize the stages of sleep.
6. List the main characteristics of REM sleep.
7. Describe the brain mechanisms of sleep and REM.
8. Discuss the consequences of the fact that sleep is controlled locally.
9. Discuss disorders of sleep.

Suppose you buy a new battery-powered toy. After you play with it for 4 hours, it suddenly stops. You wonder whether the batteries are dead or whether the toy needs repair. Later, you discover that this toy always stops after playing for 4 hours but it operates again a few hours later even without repairs or a battery change. You begin to suspect that the manufacturer inserted a device to prevent you from playing with it all day. Now you try to find that device. If you had thought that the toy stopped because it needed repairs or new batteries, you would not have asked which device turned it off.

Similarly, if we think of sleep as something like wearing out a machine, we do not ask which part of the brain produces it. But if we think of sleep as a specialized state that evolved to serve a function, we look for the mechanisms that regulate it.

Sleep and Other Interruptions of Consciousness

Let's start with some distinctions. Sleep is a state that the brain actively produces, characterized by decreased activity and decreased response to stimuli. In contrast, **coma** (KOH-muh) is an extended period of unconsciousness caused by head trauma, stroke, or disease. Someone in a coma has a low level of brain activity and no response to stimuli, not even to a strong pinch or a loud noise. Most people in a coma either die or begin to recover within a few weeks.

One step up from a coma is a condition previously known as a vegetative state, now preferably called **unresponsive wakefulness syndrome**. Someone in this condition alternates between sleep and moderate arousal, but even during the more aroused state, the person shows no awareness of surroundings and no purposeful behavior. Breathing is more regular, and a painful stimulus increases heart rate, breathing, and sweating. Eye movements occur, but they do not follow a target. The person might laugh or cry, but not in response to an external event. A **minimally conscious state** is one stage higher, with brief periods of purposeful actions and a limited amount of speech comprehension. A minimally conscious state can last for months or years.

Brain death is a condition with no sign of brain activity and no response to any stimulus. Physicians usually wait until someone has exhibited no sign of brain activity for 24 hours before pronouncing brain death, at which point most people believe it is ethical to remove life support.

Stages of Sleep

Nearly every scientific advance comes from new or improved measurements. Researchers did not even suspect that sleep has stages until they accidentally measured them, using an electroencephalograph (EEG) that records the average electrical activity near each electrode on the scalp (Figure 8.10). Figure 8.11 illustrates data from a **polysomnograph**, a combination of EEG and eye-movement records, for a college student during various stages of sleep.

Figure 8.10 Sleeping person with electrodes in place on the scalp for recording brain activity

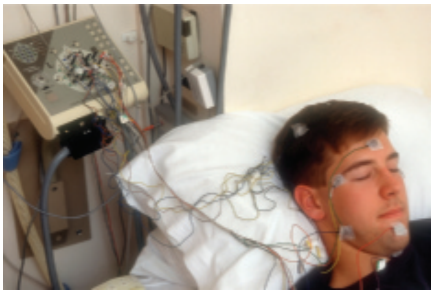

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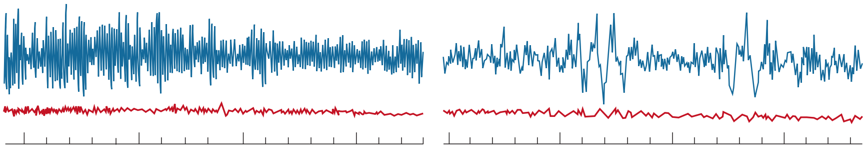
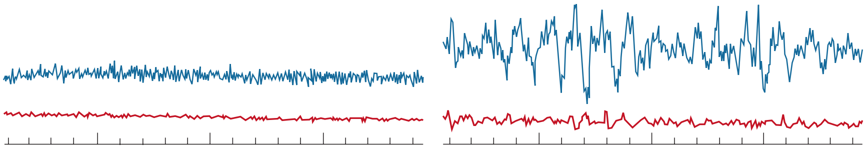
Figure 8.11 Polysomnograph records from a college student

For each of these records, the top line is the EEG from one electrode on the scalp. The middle line is a record of eye movements. The bottom line is a time marker, indicating 1-second units. Note the abundance of slow waves in slow-wave sleep.



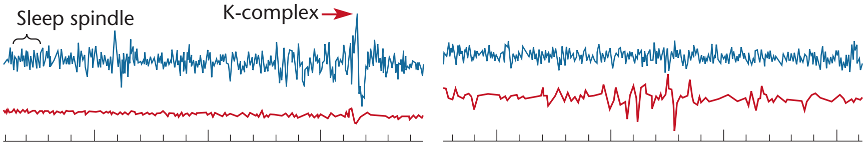
(a) Relaxed, awake

(d) Slow-wave sleep



(b) Stage 1 sleep

(e) Slow-wave sleep



(c) Stage 2 sleep

(f) REM, or "paradoxical" sleep

(**Source:** Records provided by T. E. LeVere)

Figure 8.11a presents a period of relaxed wakefulness. Note the steady series of **alpha waves** at a frequency of 8 to 12 per second. Alpha waves are characteristic of relaxation. In Figure 8.11b, sleep has just begun. During this period, stage 1 sleep, the EEG is dominated by irregular, jagged, low-voltage waves. Brain activity is less than in relaxed wakefulness but higher than in other sleep stages. Because most neurons are out of phase with one another, the EEG is full of short, rapid, choppy waves. As Figure 8.11c shows, the prominent characteristics of stage 2 are K- complexes and sleep spindles. A **K-complex** is a sharp wave associated with temporary inhibition of neuronal firing (Cash et al., 2009). A **sleep spindle** is a burst of 12- to 14-Hz waves for at least half a second. Sleep spindles result from oscillating interactions between cells in the thalamus and the cortex. Sleep spindles increase after new learning, and the number of sleep spindles correlates positively with improvements in certain types of memory (Eschenko et al., 2006; Hennies et al., 2016; Mednick et al., 2013). Evidently the sleep spindles relate to the consolidation of memory. Most people are consistent in their amount of spindle activity from one night to another, and the amount of spindle activity correlates more than 0.7 with nonverbal tests of IQ (Fogel et al., 2007). Who would have guessed that brain waves during sleep could predict IQ scores?

During **slow-wave sleep**, heart rate, breathing rate, and brain activity decrease, while slow, large-amplitude waves increase (Figures 8.11d and e). Older sources distinguished between stage 3 sleep (Figure 8.11d) with fewer slow waves, and stage 4 (Figure 8.11e) with more of them. Slow waves indicate that neuronal activity is highly synchronized. The activity is driven partly by spontaneous activity in the thalamus, and partly by waves of blood flow (Fultz et al., 2019; Gent et al., 2018).

Stop & Check

8. What do large, slow waves on an EEG indicate?

See page 279 for the answer.

Paradoxical or REM Sleep

Many discoveries occur by accident. In the 1950s, the French scientist Michel Jouvet was trying to test the learning abilities of cats after removal of the cerebral cortex. Because, as you can imagine, decorticate mammals don't do much, Jouvet recorded slight movements of the muscles and EEGs from the hindbrain. He noticed that during certain periods of apparent sleep, the cats' brain activity was relatively high, but their neck muscles were completely relaxed. Jouvet (1960) then

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recorded the same phenomenon in normal, intact cats and named it **paradoxical sleep** because it is deep sleep in some ways and light in others. (*Paradoxical* means "apparently self-contradictory.")

Meanwhile, in the United States, Nathaniel Kleitman and Eugene Aserinsky were recording eye movements to measure the onset and offset of sleep, on the assumption that eye movements stop during sleep. After someone fell asleep, they turned the machine off, because the recording paper was expensive (before the days of computers), and they did not expect to observe anything interesting in the middle of the night anyway. When they occasionally turned on the machine during the night and found evidence of eye movements, they at first assumed that something was wrong with the machine. Only after repeated careful measurements did they conclude that periods of eye movements occur during sleep (Dement, 1990). They called these periods **rapid eye movement (REM) sleep** (Aserinsky and Kleitman, 1955; Dement and Kleitman, 1957a), and they soon realized that REM sleep was synonymous with what Jouvet called paradoxical sleep. Researchers mostly use the term *REM sleep*, but they often prefer the term *paradoxical sleep* for species that lack eye movements. The stages other than REM are known as **non-REM (NREM) sleep.**

During REM sleep, the EEG shows irregular, low-voltage fast waves that indicate increased neuronal activity. In this regard, REM sleep is light and similar to stage 1, except for the eye movements, as illustrated in Figure 8.11f. However, during REM sleep, cells in the pons and medulla inhibit movement of the postural muscles, including those that support the head. In this regard, REM is deep sleep. REM is also associated with erections in males and vaginal moistening in females. Heart rate, blood pressure, breathing rate, and facial twitches fluctuate during REM more than in other stages. In short, REM sleep combines aspects of deep sleep, light sleep, and features that are difficult to classify as deep or light.

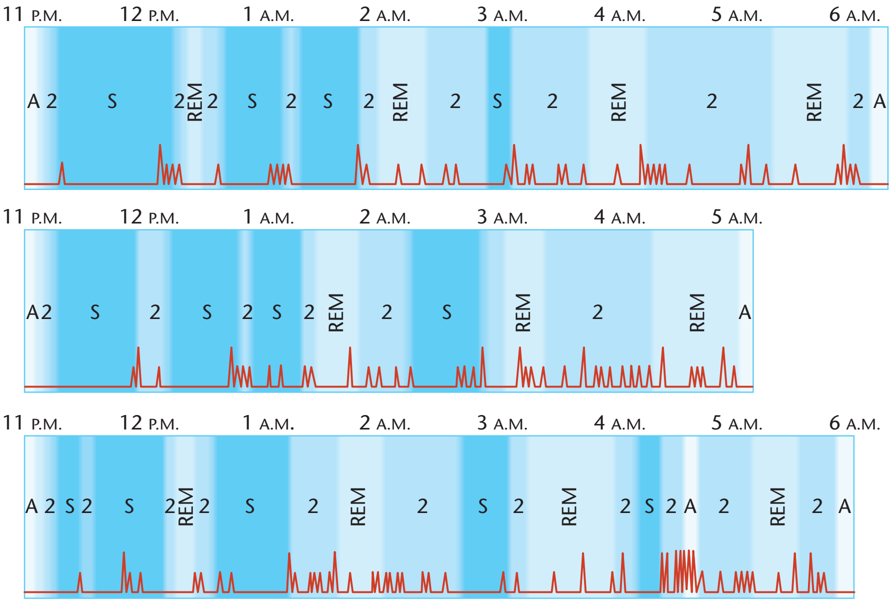
When you fall asleep, you start in stage 1 and slowly progress to stage 2 and then to slow-wave sleep, although loud noises or other intrusions can interrupt the progress. After about an hour of sleep, you begin to cycle back to stage 2 and then REM. The sequence repeats, with each cycle lasting about 90 minutes. Some people have inferred that because a cycle lasts 90 minutes, you need to sleep at least 90 minutes to get any benefit. No evidence supports that claim.

Early in the night, slow-wave sleep predominates. As time passes, REM occupies an increasing percentage of the time. Figure 8.12 represents typical sequences for young adults. The onset of REM depends on time of day more than how long you have been asleep. If you go to sleep later than usual, you still increase REM at about the same time as usual (Czeisler et al., 1980).

Figure 8.13 compares sleep for a young adult and an older adult. The older adult has less slow-wave sleep and more awakenings during the night (Scullin and Bliwise, 2015).

Figure 8.12 Sleep stages on three nights

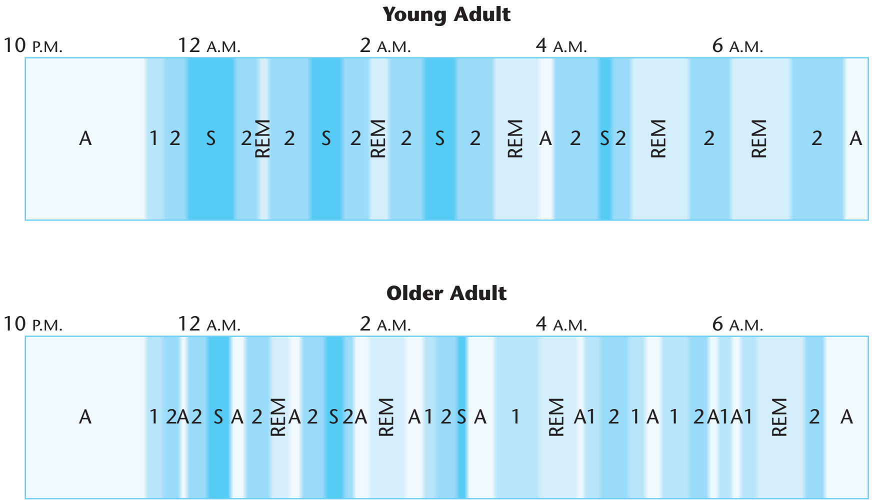
Columns indicate awake, stage 2, slow-wave sleep, and REM. Deflections in the line at the bottom of each chart indicate shifts in body position. Note that slow-wave sleep occurs mostly in the early part of the night's sleep, whereas REM sleep becomes more prevalent later.



(**Source:** Based on Dement and Kleitman, 1957a)

Figure 8.13 Typical sleep stages for a young adult and an older adult

Columns indicate awake, stage 1, stage 2, slow-wave sleep, and REM. Note that the older adult has less slow-wave sleep and frequent awakenings. Based on data from Scullin and Bliwise (2015).



That pattern is typical for most, but individual results depend on health and other factors (Mander et al., 2015).

Shortly after the discovery of REM, researchers believed it was almost synonymous with dreaming. William Dement and Nathaniel Kleitman (1957b) found that people who were awakened during REM reported dreams 80 percent to 90 percent of the time. Later research, however, found that people awakened during non-REM sleep sometimes report dreams also. REM dreams are more likely than NREM dreams to include visual imagery and complicated plots, but not always. Some people continue to report dreams despite an apparent lack of REM (Solms, 1997). In short, REM and dreaming are not the same thing, although they correlate positively.

Stop & Check

9. How can an investigator determine whether a sleeper is in REM sleep?
10. During which part of a night's sleep is REM most common?

See page 279 for the answer.

Brain Mechanisms of Wakefulness, Arousal, and Sleep

Any animal needs to regulate its level of alertness appropriate to the situation. Many brain areas participate in the control of sleep and wakefulness.

Brain Structures of Arousal and Attention

After a cut through the midbrain separates the forebrain and part of the midbrain from lower structures, an animal enters prolonged sleep for the next few days. Even after weeks of recovery, the wakeful periods are brief. We might suppose that the animal sleeps just because the cut isolated the brain from sensory stimuli. However, if a researcher cuts each individual tract that enters the medulla and spinal cord, thus depriving the midbrain of the sensory input, the animal still has normal periods of wakefulness and sleep. Evidently, the midbrain does more than just relay sensory information. It has its own mechanisms to promote wakefulness.

William Dement

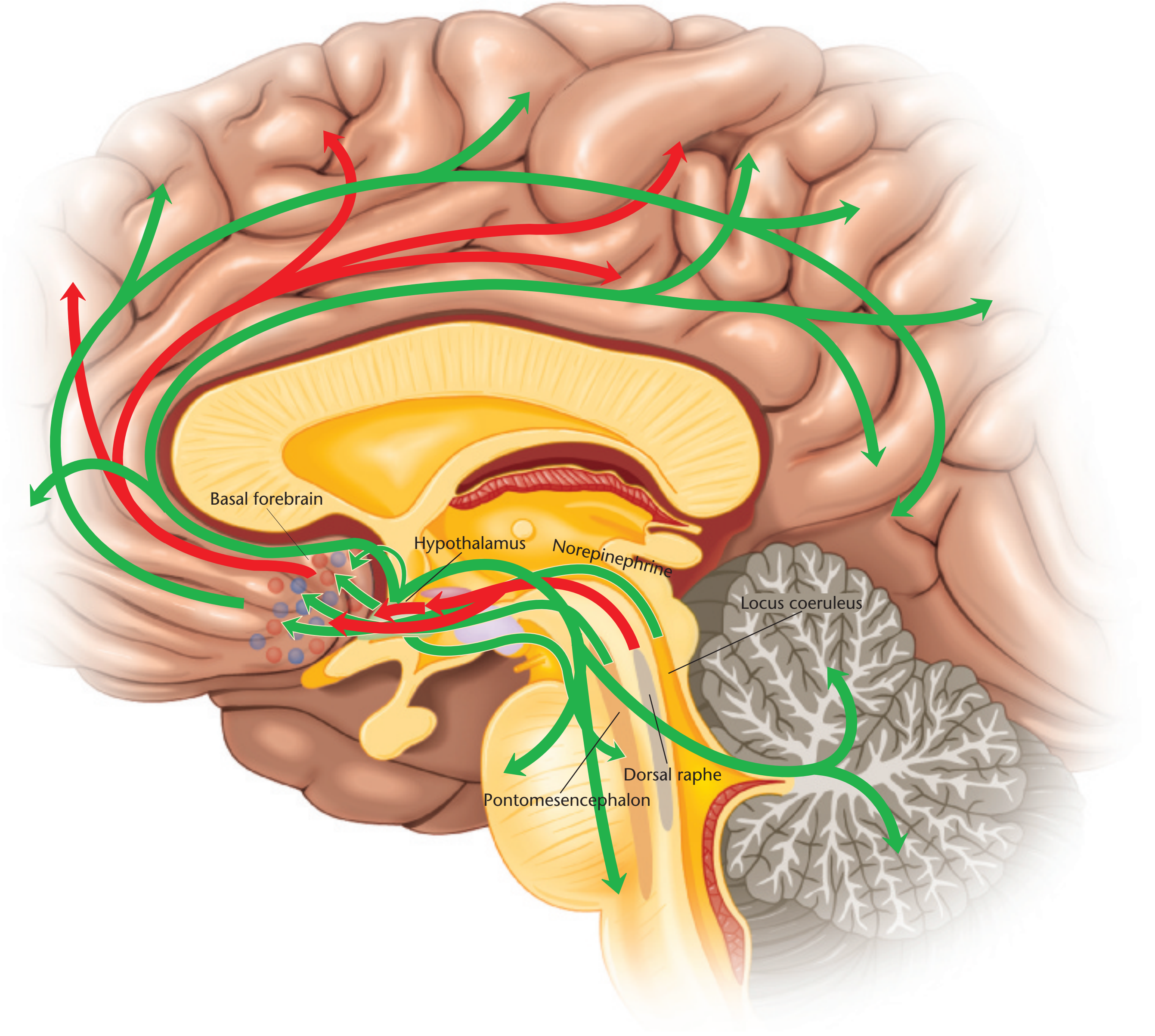
William Dement (1928–2020)

The average person would not, at first blush, pick watching people sleep as the most apparent theme for a spine-tingling scientific adventure thriller. However, there is a subtle sense of awe and mystery surrounding the "short death" we call sleep. (Dement, 1972, p. xi)

A cut through the midbrain decreases arousal by damaging the **reticular formation**, a structure that extends from the medulla into the forebrain. Some neurons of the reticular formation have axons ascending into the brain, and some have axons descending into the spinal cord. Those with axons descending into the spinal cord form part of the corticomedial tract of motor control. In 1949, Giuseppe Moruzzi and H. W. Magoun proposed that the reticular formation neurons with ascending axons are well suited to regulate arousal. The term *reticular* (based on the Latin word *rete*, meaning "net") describes the widespread connections among neurons in this system. One part of the reticular formation that contributes to cortical arousal is known as the **pontomesencephalon** (Woolf, 1996). (The term derives from *pons* and *mesencephalon*, or "midbrain.") These neurons receive input from many sensory systems and also generate spontaneous activity, varying with the circadian rhythm. Their axons extend into the forebrain (Figure 8.14). Axons from some of the cells release GABA, which inhibits behavior and promotes slow-wave sleep (Anaclet et al., 2014; Giber et al., 2015). Axons from other cells release acetylcholine, glutamate, or dopamine, producing arousal,

Figure 8.14 Brain mechanisms of sleeping and waking

Green arrows indicate excitatory connections. Red arrows indicate inhibitory connections.



(**Source:** Based on J.-S. Lin, Hou, Sakai, & Jouvet, 1996; Robbins & Everitt, 1995; Szymusiak, 1995)

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partly by regulating the levels of potassium and other ions. After the ions are in a state that supports arousal, they tend to remain at a stable concentration. For that reason, falling asleep tends to be slow (Ding et al., 2016).

The **locus coeruleus** (LOW-kus ser-ROO-lee-us; literally, "dark blue place"), a small structure in the pons, is usually inactive, especially during sleep, but it emits bursts of impulses in response to meaningful, memorable events, especially those that produce autonomic arousal or stress (Poe et al., 2020; Sterpenich et al., 2006). Axons from the locus coeruleus release norepinephrine widely throughout the cortex, so this tiny area has a huge influence. Output from the locus coeruleus increases what engineers call "gain." It increases the activity of the most active neurons and decreases the activity of less active neurons, enhancing attention to important information (Eldar et al., 2013).

The hypothalamus has both neurons that promote wakefulness and neurons that promote sleep (Chung et al., 2017; Konadhode et al., 2015). One axon pathway from the hypothalamus releases the excitatory neurotransmitter *histamine* (Lin et al., 1996), which enhances arousal and alertness (Panula and Nuutinen, 2013). Many antihistamine drugs produce drowsiness. Antihistamines that do not cross the blood–brain barrier avoid that side effect.

Another pathway from the hypothalamus releases a peptide neurotransmitter called either **orexin** or **hypocretin**. The reason for two names is that two research teams discovered this chemical almost simultaneously in 1998 and gave it different names. For simplicity, this text will stick to the term *orexin*, but if you find the term *hypocretin* elsewhere, it means the same thing. The axons releasing orexin extend from the hypothalamus to the basal forebrain and other areas, enhancing wakefulness and activity (Sakurai, 2007). Orexin is important for staying awake. Most adult humans stay awake for roughly 16 to 17 hours at a time, even when nothing much is happening. Staying awake depends on orexin, especially toward the end of the day (Lee et al., 2005). Mice lacking orexin alternate between waking and sleeping, even during an activity such as running in a running wheel (Anaclet et al., 2009). Drugs that block orexin receptors help people go to sleep (Kukkonen, 2013; Uslaner et al., 2013).

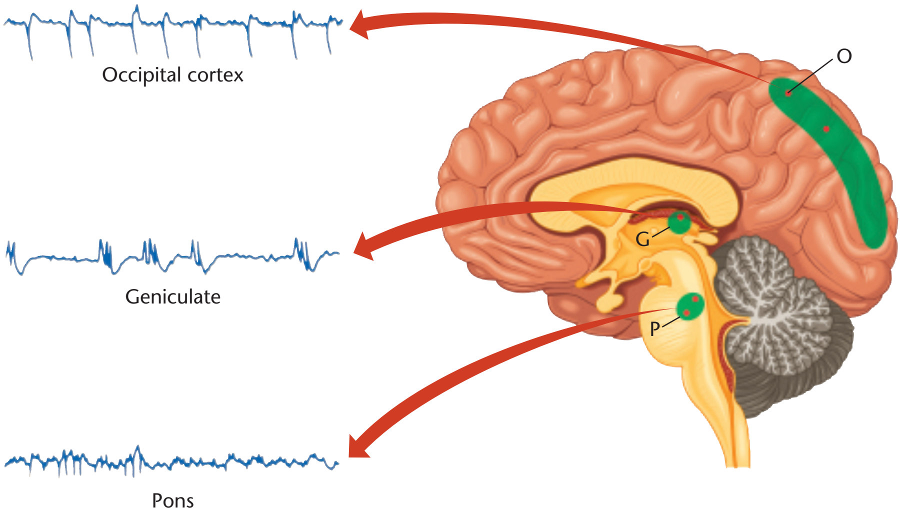
Orexin is relevant to an older person's problem of waking up in the middle of the night. In the cells that release orexin, the resting potential of the axon rises with aging and gets closer to the threshold for firing. The increased resting potential relates to a change in the potassium channels. As a result, these cells are easily excitable, causing wakefulness (Li et al., 2022).

Other pathways from the lateral hypothalamus regulate cells in the **basal forebrain** (an area just anterior and dorsal to the hypothalamus). Basal forebrain cells provide axons that extend throughout the thalamus and cerebral cortex, some of them increasing wakefulness and others inhibiting it (Xu et al., 2015) (Figure 8.14). Acetylcholine stimulates the basal forebrain cells that promote wakefulness (Zant et al., 2016). During a prolonged period of wakefulness, adenosine (one of the bases of DNA) accumulates in the basal forebrain, inhibiting those cells and increasing sleepiness (Peng et al., 2020). Caffeine increases wakefulness by inhibiting adenosine from binding to its receptors.

REM sleep is associated with a distinctive pattern of high-amplitude electrical potentials known as **PGO waves**, for pons-geniculate-occipital (Figure 8.15). Waves of neural

Figure 8.15 PGO waves

PGO waves start in the pons (P), and then are found in the lateral geniculate (G) and the occipital cortex (O). Each PGO wave is synchronized with an eye movement in REM sleep.



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activity are detected first in the pons, shortly afterward in the lateral geniculate nucleus of the thalamus, and then in the occipital cortex (Brooks and Bizzi, 1963; Laurent et al., 1974). The stimulus to start REM sleep comes from dopamine release in the amygdala (Hasegawa et al., 2022).

Stop & Check

11. Why do most antihistamines make people drowsy?
12. What would happen to the sleep–wake schedule of someone who lacked orexin?

See page 279 for the answer.

Sleep and the Inhibition of Brain Activity

During sleep, neurons in the thalamus become hyperpolarized, decreasing their response to stimuli and decreasing the information they send the cortex (Coenen, 1995). However, a moderate amount of responsiveness remains. Parents usually awaken at the sound of a crying infant. The brain responds to speech, especially by an unfamiliar voice, probably because it seems more dangerous than a familiar voice (Ameen et al., 2022; Andrillon et al., 2016).

During sleep, neurons continue firing at only a bit less than their usual spontaneous rate. How, then, do we remain unconscious? The answer is inhibition. During sleep, axons from the pons and midbrain increase their release of GABA, inhibiting the synaptic spread of information from one neuron to another (Liu et al., 2020; Massimini et al., 2005; Takata et al., 2018). When information doesn't spread, you don't become conscious of it. This point arises again in the module about consciousness.

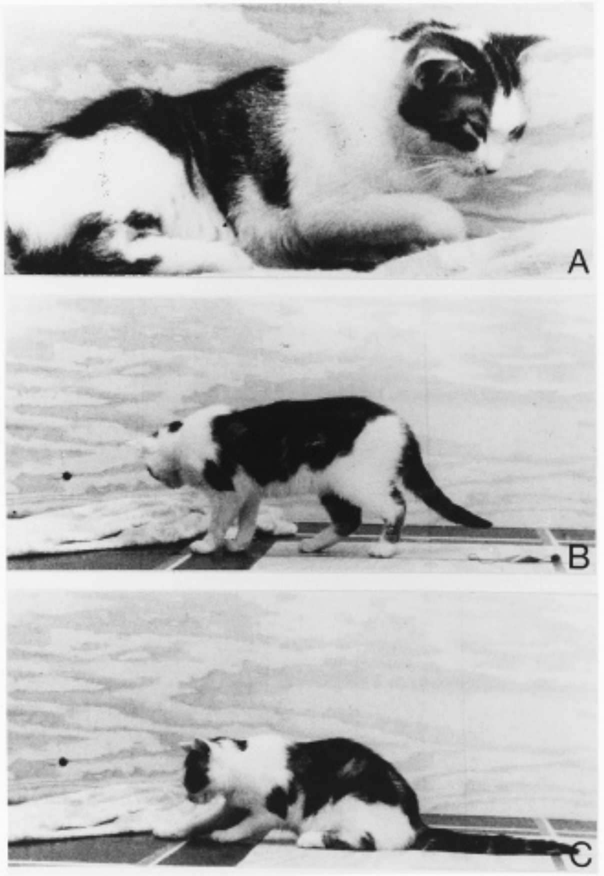
Because sleep depends on GABA-mediated inhibition, sleep can be local within the brain (Krueger et al., 2008). Brain areas usually wake up or go to sleep at nearly the same time, but not always. Thinking of sleep as a local phenomenon makes sense of some otherwise puzzling phenomena. Consider sleepwalking, also known as *somnambulism*. For sleepwalkers, much of the brain is asleep, but the motor cortex and a few other areas are awake (Terzaghi et al., 2012). Sleepwalkers generally have their eyes open, they orient to the world enough to find their way around, and they often remember some of what they did while sleepwalking, but they are confused and vulnerable, because most of the brain is not alert enough to process information and make reasonable decisions (Zadra et al., 2013).

Another example is lucid dreaming. During lucid dreaming, someone is dreaming but aware of being asleep and dreaming. Enough activity occurs in the frontal and temporal cortex to enable conscious monitoring of the dreams that the rest of the brain is generating (Voss et al., 2014). Someone having a lucid dream can control the content of the dream to some extent, as well as eye movements. In one study, young adults who had frequent lucid dreams learned to use their eye movements to signal the onset of a lucid dream. Researchers could then relate the brain activity during the dream to the content that the person described later. When people had lucid dreams about moving their hands, activity increased in the areas of motor cortex responsible for preparing for a hand movement—but not in the primary motor cortex that would have produced actual movements (Dresler et al., 2011).

Another example: Have you ever had the experience of waking up but finding that you cannot move your arms or legs? During REM sleep, cells in the pons and medulla send messages that inhibit the spinal neurons controlling the arm and leg muscles (Brooks and Peever, 2012; Uchida et al., 2021). A cat with damage to those cells moves around awkwardly during REM sleep, as if it were acting out its dreams (Morrison et al., 1995; Figure 8.16). When you awaken from an REM period, ordinarily those cells in the pons shut off and you regain muscle control, but occasionally, the rest of the brain wakes up while the pons

Figure 8.16 A cat with a lesion in the pons, wobbling about during REM sleep

Cells of an intact pons send inhibitory messages to the spinal cord neurons that control the large muscles.



(**Source:** From "Stimulus-elicited behavior in rapid eye movement sleep without atonia," by A. R. Morrison, L. D. Sanford, W. A. Ball, G. L. Mann, and R. J. Ross, 1995, *Behavioral Neuroscience, 109*, pp. 972–979. Published by APA and reprinted by permission.)

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remains in REM. The result is temporary paralysis—a disturbing experience, if you don't understand it (Cheyne and Pennycook, 2013).

Stop & Check

13. What would happen to sleeping and waking if you took a drug that blocked GABA?
14. Someone who has just awakened sometimes speaks in a loose, unconnected, illogical way. From what you just read, how could you explain this finding?

See page 279 for the answer.

Sleep Disorders

How much sleep is enough? Individuals vary genetically in their need for sleep. Mice with one genetic mutation sleep almost four hours per day longer than other mice, and if deprived of some of that extra sleep, they react just as badly as normal mice that are deprived of part of their sleep. The mutant gene increases their *need* for sleep (Funato et al., 2016). The average adult human needs 7½ to 8½ hours of sleep per night, but some have been known to do well with as little as 3 hours per night (Jones and Oswald, 1968; Meddis et al., 1973). Researchers have found families in which several people share a mutation causing them to average less than 6 hours per night. Most of them consider their condition an advantage, and they do not suffer memory problems or any of the other complaints people usually experience after sleep deprivation (Curtis et al., 2019; Shi et al., 2019; Xing et al., 2019). In short, "required sleep time" depends on your genes.

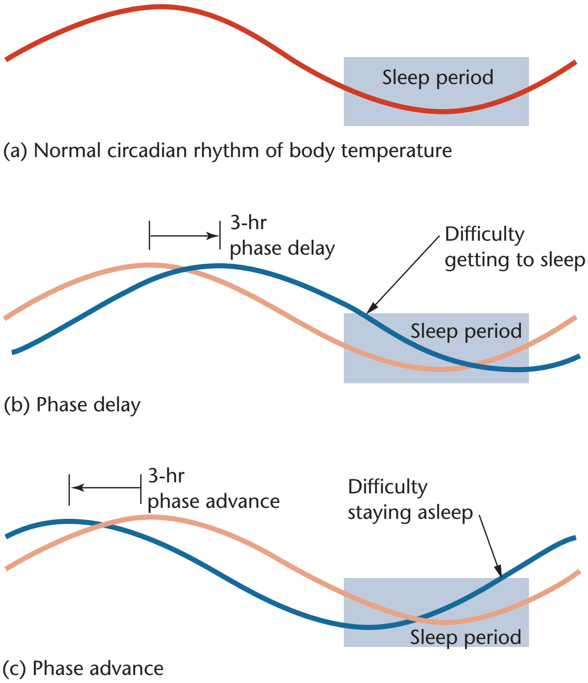
The best gauge of **insomnia**—inadequate sleep—is how you feel the next day. If you feel tired during the day, you are not sleeping enough at night. Sleep deprivation impairs memory, attention, and cognition (Scullin and Bliwise, 2015). It also magnifies unpleasant emotional reactions and increases the risk of depression (Altena et al., 2016).

Causes of insomnia include noise, uncomfortable temperatures, stress, pain, diet, and medications. Insomnia can also be the result of epilepsy, Parkinson's disease, brain tumors, depression, anxiety, or other neurological or psychiatric conditions. Some children suffer insomnia because they are milk-intolerant, and their parents, not realizing the intolerance, give them milk to drink right before bedtime (Horne, 1992). One man suffered insomnia until he realized that he dreaded going to sleep because he hated waking up to go jogging. After he switched his jogging time to late afternoon, he slept without difficulty. In short, try to identify the reason for your sleep problem before you try to solve it.

Some cases of insomnia relate to shifts in circadian rhythms (MacFarlane et al., 1985a, 1985b). Ordinarily, people fall asleep while their temperature is declining and awaken while it is rising, as in Figure 8.17a. Someone whose rhythm is *phase delayed*, as in Figure 8.17b, has trouble falling asleep at the usual time, as if the hypothalamus thinks it isn't late enough (Morris et al., 1990). Someone whose rhythm is *phase advanced*, as in Figure 8.17c, falls asleep easily but awakens early.

Figure 8.17 Insomnia and circadian rhythms

People with a phase delay have trouble getting to sleep. People with a phase advance have trouble staying asleep.



(a) Normal circadian rhythm of body temperature

(b) Phase delay

(c) Phase advance

Another cause of insomnia is, paradoxically, the use of sleeping pills. Frequent use causes dependence and an inability to sleep without the pills (Kales et al., 1978). For most people, drinking coffee during the evening interferes with sleep. Coffee also phase-delays the circadian rhythm, delaying the release of melatonin (Burke et al., 2015). Ordinarily that delay causes problems, although it might help combat jet lag after traveling west.

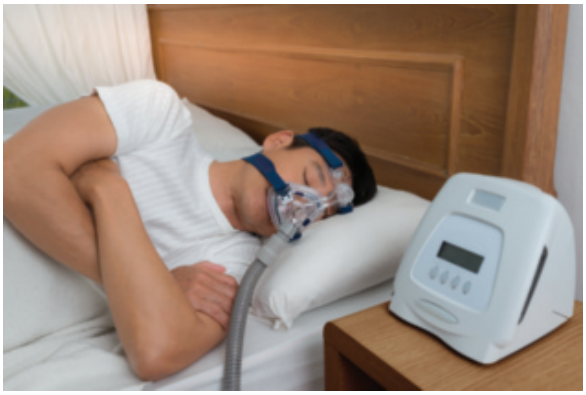
Sleep Apnea

One type of insomnia is **sleep apnea**, impaired ability to breathe while sleeping. People with sleep apnea have breathless periods of a minute or so from which they awaken gasping for breath. They may not remember their awakenings, although they certainly notice the consequences, such as sleepiness and impaired attention the following day. Prolonged sleep apnea leads to a loss of neurons, with an impairment of learning and other functions (Beebe and Gozal, 2002; Macey et al., 2002).

Sleep apnea is often related to obesity, especially in middle-aged men. Many men with obesity have narrower than normal airways and have to compensate by breathing frequently or vigorously. During sleep, they cannot keep up

Figure 8.18 A continuous positive airway pressure (CPAP) mask

The mask fits snugly over the nose and delivers air at a fixed pressure, strong enough to keep the breathing passages open.



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that rate of breathing. Furthermore, their airways become even narrower than usual when they adopt a sleeping posture (Mezzanotte et al., 1992).

People with sleep apnea are advised to lose weight and avoid alcohol and tranquilizers (which relax the breathing muscles). The most common treatment is a mask that covers the nose and delivers air under enough pressure to keep the breathing passages open (Figure 8.18). That procedure improves sleep and blood pressure, but it only slightly decreases the risk of stroke or heart attack, probably because many people continue to be overweight (Guo et al., 2016). Unfortunately, the device is uncomfortable, and many people refuse to continue wearing it. Surgery to open the breathing spaces can be helpful in some cases, but disappointing in others. Several drugs have demonstrated mild to moderate benefits (Schütz et al., 2021).

Stop & Check

15. What kinds of people are most likely to develop sleep apnea?

See page 279 for the answer.

Narcolepsy

Narcolepsy, a condition characterized by periods of sudden sleepiness during the day, affects about 1 person in 1,000. It sometimes runs in families, but most cases emerge in people with no affected relatives. Narcolepsy has four main symptoms, although not every patient has all four. Each of these symptoms can be interpreted as an intrusion of a REM-like state into wakefulness:

1. Attacks of sleepiness during the day.
2. Occasional cataplexy—an attack of muscle weakness while the person remains awake. Cataplexy is often triggered by strong emotions, such as anger or great excitement. One man suddenly collapsed during his wedding ceremony. The amygdala, important for emotional processing, is active at the start of a REM period and at a narcoleptic attack (Hasegawa et al., 2022).
3. Sleep paralysis—an inability to move while falling asleep or waking up. Many people have experienced sleep paralysis occasionally, but people with narcolepsy experience it frequently.
4. Hypnagogic hallucinations—dreamlike experiences that the person has trouble distinguishing from reality, often at the onset of sleep.

The cause relates to a loss of the hypothalamic cells that release orexin (Thannickal et al., 2000). In many cases it appears to be an autoimmune reaction, in which the immune system has attacked those cells (Latorre et al., 2018; Mahoney et al., 2019). The H1N1 flu virus in 2009–2010 caused many cases of narcolepsy by strongly activating the immune system (Tesoriero et al., 2016). Narcolepsy is unique among behavioral disorders as it is the only one linked to a biochemical marker (low orexin levels) that is reliable enough to establish the diagnosis. Using that marker is more trouble than it is worth, however, because narcolepsy is easy to identify from behavior alone.

Recall that orexin is important for maintaining wakefulness. People lacking orexin alternate between short waking periods and short sleepy periods, instead of staying awake throughout the day. Mice that lack orexin and dogs that lack orexin receptors have symptoms much like human narcolepsy, with frequent alternations between wakefulness and sleep (Hara, 2001; Lin et al., 1999; Mochizuki et al., 2004).

The most common treatment so far is stimulant drugs that enhance dopamine and norepinephrine activity, although antidepressants and several other drugs also help in some cases (Thorpy and Bogan, 2020). Orexin itself is not an option, because it does not readily cross the blood–brain barrier, but clinical trials have begun with drugs that activate orexin receptors. Animal research has found that prolonged use of opiates can increase the production of orexin, even in mice engineered to develop narcolepsy (Thannickal et al., 2018). Physicians have been understandably reluctant to try this approach with humans. The fact that opiates prompt orexin release in narcoleptic mice implies that the cells responsible for orexin release were not dead, just inactive.

Stop & Check

16. What is the relationship between orexin and narcolepsy?

See page 279 for the answer.

Periodic Limb Movement Disorder and REM Behavior Disorder

Another problem is **periodic limb movement disorder**, characterized by repeated involuntary movement of the legs or arms during sleep. It is distinct from restless leg syndrome, in which people often feel an urge to kick even while awake.

Many people, perhaps most, experience an occasional involuntary kick, especially when starting to fall asleep. Leg movements are not a problem unless they become persistent. In people with periodic limb movement disorder, mostly middle-aged and older, the legs kick once every 20 to 30 seconds for minutes or hours, mostly during NREM sleep.

For most people, the postural muscles are relaxed and inactive during REM sleep. However, people with **REM behavior disorder** move around vigorously during their REM periods, apparently acting out their dreams. They frequently dream about defending themselves against attack, and they may punch, kick, and leap about. They often injure themselves or other people and damage property (Olson et al., 2000).

Night Terrors and Sleepwalking

A **night terror** is an experience of intense anxiety from which a person awakens screaming in terror. It is more severe than a nightmare, which is simply an unpleasant dream. Night terrors occur during NREM sleep and are more common in children than adults. Dream content, if any, is usually simple, such as a single image.

Sleepwalking runs in families and occurs mostly in children. Most people who sleepwalk, and many of their relatives, have additional sleep difficulties such as chronic snoring, disordered sleep breathing, bed-wetting, and night terrors (Cao and Guilleminault, 2010). The causes of sleepwalking are not well understood, but it is more common when people are sleep deprived or under unusual stress (Zadra and Pilon, 2008). It is most common during slow-wave sleep early in the night. It does not occur during REM sleep, when the large muscles are completely relaxed. Sleepwalking is usually harmless but not always. One teenage girl walked out of her house, climbed a crane, and went back to sleep on a support beam. Fortunately, a pedestrian saw her and called the police. Sleepwalkers have been known to eat, rearrange furniture, fall off balconies, and drive cars—while disregarding lanes and traffic lights. The deeds of sleepwalkers are poorly planned and usually not remembered. Evidently, some parts of the brain are awake and other parts are asleep (Gunn and Gunn, 2007). Contrary to common sayings, it is not dangerous to awaken a sleepwalker. It is also not helpful.

An analogous condition is sleep sex or "sexsomnia," in which sleeping people engage in sexual behavior, either with a partner or by masturbation, and do not remember it afterward. Some cases occur when someone with sleep apnea awakens partially. Many people with sexsomnia also sleepwalked as children. Overall, the condition is not well understood (Schenck, 2015).

Sexsomnia poses a threat to romances and marriages. As one woman said, "After getting married a few years ago, my husband told me I was masturbating in my sleep. I was mortified, thinking back to all the slumber parties as a girl, and then when I was older and my little sister stayed the night at my house! How many others might have witnessed and not said anything? My new marriage is on the rocks, since I'm having such good sex in my sleep, I have NO desire while I'm awake. This is killing my relationship with my husband" (Mangan, 2004, p. 290).

Module 8.2 | In Closing

Stages of Sleep

The discovery of stages of sleep was a major landmark in psychology because researchers found a previously unrecognized distinction that is both biologically and psychologically important. It also demonstrated that external measurements—in this case, EEG recordings—can be used to identify internal experiences. We now take it largely for granted that an electrical or magnetic recording from the brain can tell us something about a person's experience, but it is worth pausing to note what a surprising discovery that was in its time.

Summary

1. During sleep, brain activity decreases, but a stimulus can awaken the person. Someone in a coma cannot be awakened. An unresponsive wakefulness syndrome or minimally conscious state can last months or years, during which the person shows only limited responses. Brain death is a condition without brain activity or responsiveness of any kind. **269**

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2. Over the course of about 90 minutes, a sleeper goes through stages 1, 2, and slow-wave sleep and then returns through stage 2 to a stage called REM (rapid eye movement sleep). **269**
3. REM sleep or paradoxical sleep is a condition marked by rapid eye movements, more cortical activity than other sleep, relaxation of the body's postural muscles, and an increased probability of dreams. **270**
4. The brain has multiple systems for arousal. The pontomesencephalon, hypothalamus, and basal forebrain include some neurons that promote wakefulness and others that promote sleep. **272**
5. The locus coeruleus is active in response to meaningful events. It facilitates attention and new learning. **274**
6. Orexin is a peptide that maintains wakefulness. **274**
7. During sleep, enhanced release of GABA limits neuronal activity and blocks the spread of activation. Because this suppression can be stronger in one brain area than another, it is possible for part of the brain to be more awake than another. **275**
8. People with sleep apnea have long periods without breathing while they sleep. So far, no treatment are fully satisfactory. **276**
9. People with narcolepsy have attacks of sleepiness during the day. Narcolepsy is associated with a deficiency of the neurotransmitter orexin. **277**
10. Sleepwalking and sexsomnia are cases of somewhat purposeful, somewhat confused behaviors during partial arousal from sleep. The person is unlikely to remember the episode later. **278**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

alpha waves **270**
basal forebrain **274**
brain death **269**
coma **269**
insomnia **276**
K-complex **270**
locus coeruleus **274**
minimally conscious state **269**
narcolepsy **277**
night terrors **278**
non-REM (NREM) sleep **271**
orexin (or hypocretin) **274**
paradoxical sleep **271**
periodic limb movement disorder **277**
PGO waves **274**
polysomnograph **269**
pontomesencephalon **273**
rapid eye movement (REM) sleep **271**
REM behavior disorder **278**
reticular formation **273**
sleep apnea **276**
sleep spindle **270**
slow-wave sleep (SWS) **270**
unresponsive wakefulness syndrome **269**

Thought Question

Unlike adults, infants alternate between short waking periods and short naps. What can we infer about their neurotransmitters?

Stop & Check Answers

8. Large, slow waves indicate a low level of activity, with much synchrony among neurons.
9. Examine EEG pattern and eye movements.
10. REM becomes most common toward the end of the night's sleep.
11. A pathway from the hypothalamus uses histamine as its neurotransmitter to increase arousal. Antihistamines that cross the blood–brain barrier block those synapses.
12. Someone without orexin would alternate between brief periods of waking and sleeping.
13. You would remain awake longer than usual.
14. People often awaken from a REM period, because REM is abundant toward morning when people usually awaken. Shortly after awakening, certain brain areas may still be in a REM-like state, and thinking may have an illogical, dreamlike quality.
15. Sleep apnea is most common among overweight middle-aged men.
16. Orexin is important for staying awake. Therefore, people or animals lacking either orexin or the receptors for orexin develop narcolepsy, characterized by bouts of sleepiness during the day.

Module 8.2 | End-of-Module Quiz

1. What do alpha waves (8–12 Hz) indicate?
   - **a.** Excitation
   - **b.** Relaxation
   - **c.** Deep sleep
   - **d.** Coma

2. What causes the sleep spindles in stage 2 sleep?
- **a.** Exchange of information between thalamus and cortex
- **b.** Messages from the pons to inhibit the postural muscles
- **c.** Defense mechanisms against anxiety
- **d.** Control of body temperature

3. What do the high-amplitude slow waves of slow-wave sleep indicate?
- **a.** An increased level of brain activity
- **b.** Synchrony among neurons
- **c.** Muscle contractions
- **d.** Responses to sensory stimulation

4. Why is REM sleep also known as paradoxical sleep?
- **a.** Activity in the left hemisphere does not match the activity in the right hemisphere.
- **b.** It differs from other sleep behaviorally, despite equal brain activity.
- **c.** It is deep sleep in some ways and light in others.
- **d.** Because a pair of docs discovered it.

5. At which time, if any, is REM sleep most common?
- **a.** During the early part of the night's sleep
- **b.** During the middle of the night's sleep
- **c.** Near the end of the night's sleep
- **d.** During all parts equally

6. How does the sleep of older adults differ from that of young adults?
- **a.** Older adults have less slow-wave sleep and more awakenings.
- **b.** Older adults have more slow-wave sleep and more awakenings.
- **c.** Older adults have less slow-wave sleep and fewer awakenings.
- **d.** Older adults have more slow-wave sleep and fewer awakenings.

7. Activating the locus coeruleus increases which of the following?
- **a.** Sleep
- **b.** Attention
- **c.** Hunger
- **d.** Sexual desire

8. What is the role of orexin in wakefulness and sleep?
- **a.** It stimulates REM sleep.
- **b.** It stimulates NREM sleep.
- **c.** It helps someone stay awake.
- **d.** It is active during switches back and forth between wakefulness and sleep.

9. Why are people unconscious during slow-wave sleep?
- **a.** Inhibitory transmitters block the spread of activity in the cortex.
- **b.** The sensory receptors become unresponsive to nearly all input.
- **c.** Spontaneous activity ceases in the neurons of the cortex.
- **d.** Circulating hormones block the sodium gates in axon membranes.

10. If a person awakens but find they temporarily cannot move their arms or legs, what is happening?
- **a.** They are probably developing a neurological disease.
- **b.** Their muscles do not have enough sodium.
- **c.** They need more time to get the blood flowing to their muscles.
- **d.** Most of their brain is awake, but part of their pons and medulla remain in REM sleep.

11. Which of the following groups of individuals is most likely to develop sleep apnea?
- **a.** Overweight men
- **b.** Women recovering from anorexia nervosa
- **c.** Children
- **d.** Vegetarians

12. Narcolepsy is linked to a deficit of which neurotransmitter?
- **a.** Dopamine
- **b.** GABA
- **c.** Orexin
- **d.** Acetylcholine

Answers: 1b, 2a, 3b, 4c, 5c, 6a, 7b, 8c, 9a, 10d, 11a, 12c.

Module 8.3

Why Sleep? Why REM? Why Dreams?

Learning Objectives

After studying this module, you should be able to:

10. Evaluate possible explanations of the functions of sleep.
11. Describe species differences in sleep.
12. Evaluate possible explanations of the functions of REM.
13. Describe possible explanations of dreaming.

Why do you sleep? "That's easy," you reply. "I sleep because I get tired." Well, yes, but it is not the same as muscle fatigue. You need almost as much sleep after a day of sitting around the house as after a day of intense physical or mental activity (Horne and Minard, 1985; Shapiro et al., 1981). Furthermore, you could rest your muscles while staying awake.

You feel tired at the end of the day because inhibitory processes in your brain decrease your arousal. We evolved mechanisms to cause sleep. Why?

Functions of Sleep

Sleep serves many functions. During sleep, we rest our muscles and decrease metabolism. We reorganize synapses and strengthen memories. Fluid drains from the brain and spinal cord into the subarachnoid space, removing potentially harmful proteins and waste products (Fultz et al., 2019; Nedergaard and Goldman, 2020).

People who don't get enough sleep react more severely than average to stressful events (Minkel et al., 2012). Their mental health may suffer (van der Kloet et al., 2012). Inadequate sleep is a major cause of accidents by workers and poor performance by college students. Driving while sleep deprived is comparable to driving under the influence of alcohol (Falleti et al., 2003). Even one night of sleeplessness activates the immune system, as if you were ill (Matsumoto et al., 2001). Clearly, we need sleep. Is there, however, an original reason?

Sleep and Energy Conservation

Even if we agreed on what is the most important function of sleep for humans today, it might not be the function for which sleep originally evolved. By analogy, what is the main function of computers? You might use a computer to write papers, send email, search the Internet, play video games, store and display photographs, play music, or find a date. All of those are valuable functions, but the original purpose of computers was to do mathematical calculations. Similarly, sleep probably started with a simple function to which evolution added others later. Even bacteria and jellyfish have circadian rhythms of activity and inactivity (Mihalcescu et al., 2004; Nath et al., 2017). What is the benefit of sleep to all species, even those with little or no nervous system?

A likely hypothesis is that sleep's original function, and still an important one, is to save energy (Anafi et al., 2019; Kleitman, 1963; Siegel, 2009, 2012). Nearly every species is more efficient at some times of day than at others. Those with good vision are more efficient in the day. Those that rely on other senses are more efficient at night, when their predators cannot see them. Sleep conserves energy during the times when activity would be ineffective and possibly dangerous. When NASA built the Rover spacecraft to explore Mars, they included a mechanism to make it "sleep" at night to conserve the batteries.

During sleep, a mammal's body temperature decreases by 1° or 2° C, enough to save a noticeable amount of energy. It drops even more in some birds, especially hummingbirds. Muscle activity decreases, saving more energy. Animals increase their sleep duration during food shortages, when energy conservation is especially important (Berger and Phillips, 1995).

Sleep is therefore in some ways analogous to hibernation. Hibernation is a true need. A ground squirrel that is prevented from hibernating becomes as disturbed as a person who is prevented from sleeping. The function of hibernation is simply to conserve energy while food is scarce.

Analogous to Sleep: Hibernation

Hibernating animals decrease their body temperature, usually maintaining it just slightly above that of the environment, but always warm enough to prevent the blood from freezing. Heart rate and brain activity drop to almost nothing, neuron cell bodies shrink, and many synapses disappear, regenerating at the end of hibernation (Peretti et al., 2015). Here are a few curious facts about hibernation:

1. Whether or not bears hibernate is a matter of definition. Bears sleep most of the winter, lowering their body temperature a few degrees and decreasing their metabolism

and heart rate (Tøien et al., 2011), but their state is not as extreme as that of smaller hibernators such as bats and ground squirrels.

2. Hamsters also hibernate, and pet stores generally do not tell people about it. If you keep your pet hamster in a cool, dimly lit place during the winter, and it appears to have died, make sure that it is not just hibernating before you bury it! (Or did I tell you that too late?)
3. Hibernating animals come out of hibernation for a few hours, once every few days or few weeks, depending on the species. Still, they spend most of this nonhibernating time asleep (Barnes, 1996; Williams et al., 2012).
4. Hibernation retards or suspends the aging process. Hamsters that spend longer times hibernating have proportionately longer life expectancies than other hamsters do (Lyman et al., 1981). Fat-tailed dwarf lemurs, which hibernate, survive years longer than related species of the same size that do not hibernate (Blanco and Zehr, 2015). Hibernation is also a period of relative invulnerability to infection and trauma. Procedures that would ordinarily damage the brain, such as inserting a needle into it, produce little if any harm during hibernation (Zhou et al., 2001).

Species Differences in Sleep

If one of the main functions of sleep is to decrease activity at times of relative inefficiency, we might expect to find little or no sleep in species that are equally effective at all times of day. Indeed, evidence supports that expectation. Mexican cavefish have one population that lives in normal waters subject to alternations of day and night, and other populations that evolved to live in caves with no light and virtually constant temperature. In contrast to the fish in normal waters, which average more than 13 hours of sleep per day, the populations in caves have only 2 to 4 hours of sleep per day without a circadian rhythm (Duboué and Keene, 2016; Duboué et al., 2011; Kavanau, 1998; Moran et al., 2014). Many animals that live near the North or South Pole greatly decrease their sleep during summer, when the sun is constantly above the horizon. While male sandpipers are competing for mates above the Arctic Circle, many of them are active up to 23 hours per day for nearly three weeks, with no apparent harm to their health or alertness (Lesku et al., 2012). Many reindeer and penguins have long periods of nearly constant wakefulness (Bloch et al., 2013).

Other species decrease their sleep under certain circumstances. After a dolphin or whale gives birth, both mother and baby stay awake 24 hours a day for the first couple of weeks while the baby is especially vulnerable. Neither shows any sign of harm from sleep deprivation (Lyamin et al., 2005). Two elephant matriarchs, who take charge of protecting their troops, were observed to sleep two hours or less per night (Gravett et al., 2017).

Alan Williams/Alamy Stock Photo

A European swift

Dolphins, whales, and other aquatic mammals always face the problem of needing to surface periodically for a breath of air. To do so, they evolved the ability to sleep on one side of the brain at a time. The two hemispheres take turns sleeping, always leaving one alert enough to control swimming and breathing (Rattenborg et al., 2000). Seals also sleep in one hemisphere at a time when they are at sea, although they sleep in both hemispheres when they are on land (Lyamin et al., 2008).

Swifts are small birds that chase insects. They get all the nutrition and water they need from the insects. When a baby European swift first takes off from its nest, how long would you guess its first flight lasts, until it comes to land again?

The answer: up to 2 years. Except during treacherous storms, the bird doesn't land on solid ground until it is old enough to mate and build a nest. In the meantime, it spends its life in the air. At night it heads into the wind, sticks out its wings, and glides (Bäckman and Alerstam, 2001). Does it fly while asleep? Does it sleep with one hemisphere at a time? Or has it abandoned sleep altogether? Answering these questions would require recording EEG from a flying bird that is not much bigger than a house sparrow. Good luck with that one. Measuring EEG is more feasible in great frigate birds, which fly over the ocean for weeks or months at a time, eating flying fish, flying squid (yes, there is such a thing), and anything else that comes to the surface. These large birds never land on the water, because their feathers would become waterlogged and prevent them from taking flight again. So, they spend the night in the air. EEG records indicate that they have periods of slow-wave sleep in one hemisphere at a time, and REM periods in both hemispheres. Moreover, their sleep episodes last an average of only 11 seconds, with a total of less than 45 minutes per night. When they come on land to nest and rear young, they sleep 12 or more hours per day (Rattenborg et al., 2016). They need almost constant alertness while flying at sea, but not while sitting on a nest.

Migrating birds face a problem: During a week or two in fall and spring, they forage for food during the day and do their migratory flying at night, leaving them little

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A great frigate bird

Jo Ellen Kalat

The lion sleeps tonight… and maybe part of the morning… and much of the afternoon, too.

time for sleep. They apparently decrease their need for sleep during migration. If a bird is kept in a cage during the migration season, it flutters around restlessly at night, sleeping only a third of its usual amount. It compensates to some extent with brief drowsy periods (less than 30 seconds each) during the day (Fuchs et al., 2006). Still, it gets little sleep, while remaining alert and performing normally on learning tasks. If the same bird is deprived of sleep during other seasons of the year, its performance suffers (Rattenborg et al., 2004). Exactly how a mother dolphin, elephant matriarch, great frigate bird, or migratory bird decreases its sleep need is unknown, but the fact that it is possible fits with the idea that sleep is largely a way to conserve energy, and that the other functions of sleep can be performed briefly.

Variations in animals' sleep habits make sense in terms of their eating habits and their need for defense (Allison and Cicchetti, 1976; Campbell and Tobler, 1984). Grazing animals that need to eat for many hours per day get less sleep than carnivores (meat eaters) that satisfy their nutritional needs with a single meal. Animals that need to be on the alert for predators get little sleep, whereas the predators themselves sleep easily. Insect-eating bats are active in the early evening, when moths and similar insects are most abundant, and then they sleep the rest of the day (Figure 8.19).

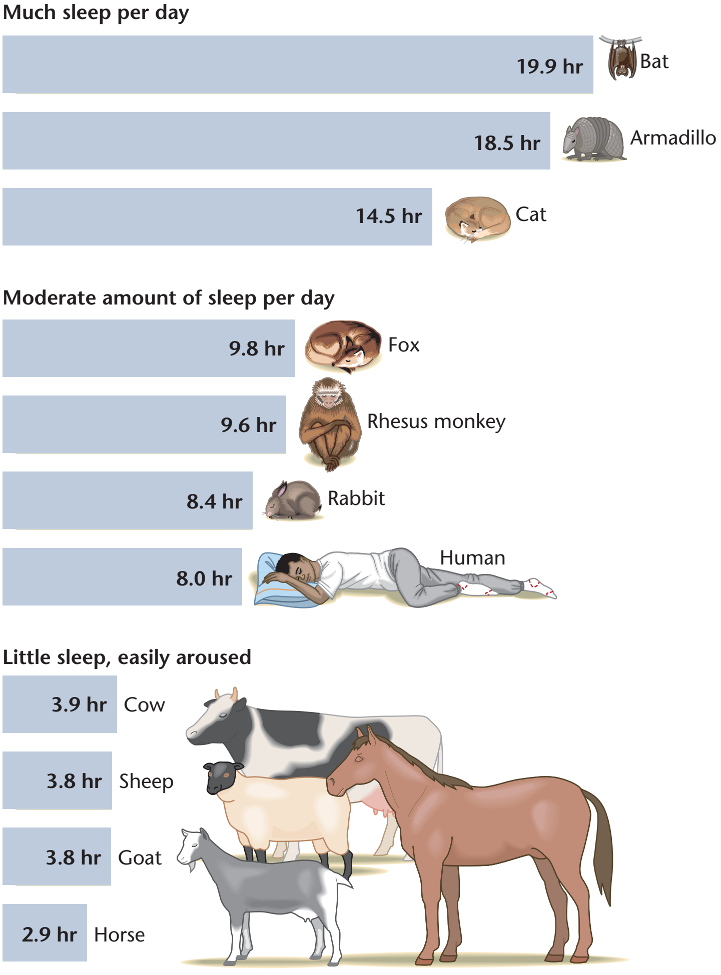
Stop & Check

17. What might one predict about the sleep of fish that live deep in the ocean?
18. What kind of animal tends to get more than the average amount of sleep?

See page 287 for the answer.

Figure 8.19 Hours of sleep per day for various species

Animals that are safe when they sleep tend to sleep more than animals that are in danger of being attacked while they sleep.



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Sleep and Memory

Another function of sleep is improved memory. If you do not get a good night's sleep, your memory and cognition will suffer the next day (Appleman et al., 2016; Yoo et al., 2007). In contrast, if you learn something and then go to sleep, even a nap, your memory solidifies and may become better than it was before sleep (Hu et al., 2006; Korman et al., 2007; Nettersheim et al., 2015; Payne et al., 2015). In one study, students memorized a vocabulary list in Swahili until they had said each item correctly just once. Then 12 hours later they tried again. Those who learned the list in the morning and tried again in the evening had forgotten most of the words. Those who learned in the evening, slept, and tried again in the morning did better (Mazza et al., 2016). So, if you want to memorize something, study it before going to sleep. Better yet, study before sleep and review after you awaken.

Sleep also helps people reanalyze their memories: In one study, people who had just practiced a complex task were more likely to perceive a hidden rule (an "aha" experience) after a period of sleep than after a similar period of wakefulness (Wagner et al., 2004). Another study found that a nap that included REM sleep enhanced performance on certain kinds of creative problem solving (Cai et al., 2009). Both REM sleep and slow-wave sleep have been linked to strengthening of memories (Boyce et al., 2016; Gais et al., 2000; Plihal and Born, 1997; Wei et al., 2016).

How does sleep enhance memory? Researchers recorded activity in the hippocampus during learning, and then recorded from the same locations during sleep, using microelectrodes within cells for laboratory animals and electrodes on the scalp for humans. The results: Patterns that occurred during sleep resembled those that had occurred during learning, except that they were more rapid during sleep. Furthermore, the amount of hippocampal activity during sleep correlated highly with the subsequent improvement in performance (Derégnaucourt et al., 2005; Euston et al., 2007; Huber et al., 2004; Ji and Wilson, 2007; Maquet et al., 2000; Peigneux et al., 2004). As the brain replays its experiences during sleep it forms new dendritic branches that strengthen the memories (Yang et al., 2014). Knowledge storage depends on highly synchronized *sharp wave ripples* that transfer information from the hippocampus or thalamus to the parietal and frontal cortex. This happens both during sleep and during relaxed wakefulness (Crunelli et al., 2018; Higgins et al., 2021; Karlsson and Frank, 2009; Khodagholy et al., 2017).

An important way for sleep to strengthen memory is by weeding out the less successful connections. If your brain strengthened synapses every time it learned something, without removing or weakening other synapses, the result might be runaway overactivity, or it might resemble the clutter in a room where you kept adding things without ever removing anything. Research by Gina Poe and others has found that the brain conditions during sleep are ideal for pruning ineffective synapses and deleting unimportant memories (Li et al., 2017; Poe, 2017).

Stop & Check

19. How does sleep improve memory?

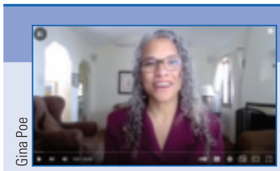
See page 287 for the answer.

Functions of REM Sleep

On average, people spend about a third of their life asleep and about a fifth of sleep in REM, totaling about 600 hours of REM per year. Presumably, REM serves a biological function. But what is it?

One way to approach this question is to compare the people or animals with more REM to those with less. REM sleep is widespread in mammals and birds, indicating that it is part of our ancient evolutionary heritage. Some species, however, have far more than others. As a rule, the species with the most total sleep hours also have the highest percentage of REM sleep (Siegel, 1995). Cats spend up to 16 hours a day sleeping, much or most of it in REM sleep. Rabbits, guinea pigs, and sheep sleep less and spend little time in REM.

Figure 8.20 illustrates the relationship between age and REM sleep for humans. Infants get more REM and more total sleep than adults do. Among young adults, those who sleep 9 or more hours per night have the highest percentage of REM sleep, and those who sleep 5 or fewer hours have the least percentage. This pattern implies that although REM is no doubt important, NREM is more



Gina Poe

Gina Poe

Sleep is essential for the targeted, careful forgetting necessary for experience-dependent synaptic circuit reshaping during development and throughout the lifespan. (Poe, 2017, p. 471)

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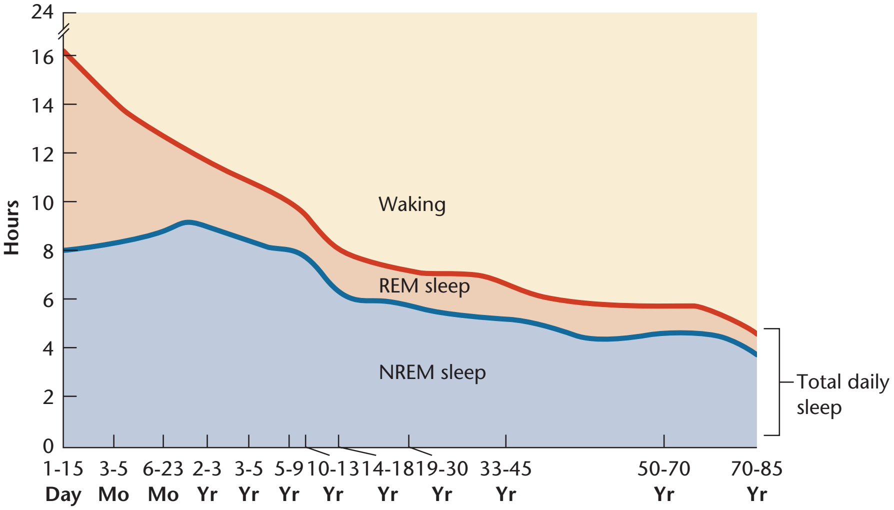
Figure 8.20 Sleep patterns for people of various ages

REM sleep occupies about 8 hours a day in newborns but less than 2 hours in most adults. The sleep of infants is not quite like that of adults, however, and the criteria for identifying REM sleep are not the same.



(**Source:** From "Ontogenetic development of human sleep-dream cycle," by H. P. Roffwarg, J. N. Muzio, and W. C. Dement, 1966, *Science, 152*, pp. 604–609. Copyright 1966 AAAS. Reprinted by permission.)

tightly regulated. The amount of NREM varies less among individuals and among species.

One hypothesis is that REM is important for strengthening memory (Crick and Mitchison, 1983). However, although memory consolidation does occur during REM, many people take antidepressant drugs that severely decrease REM sleep without causing memory problems (Rasch et al., 2009).

Another hypothesis sounds odd because we tend to imagine a glamorous role for REM sleep: David Maurice (1998) proposed that REM just shakes the eyeballs back and forth enough to get sufficient oxygen to the corneas of the eyes. The corneas, unlike the rest of the body, get oxygen directly from the surrounding air. During sleep, because they are shielded from the air, they deteriorate slightly (Hoffmann and Curio, 2003). They do get some oxygen from the fluid behind them, but when the eyes are motionless, that fluid becomes stagnant. Moving the eyes increases the oxygen supply to the corneas. According to this view, REM is a way of arousing a sleeper just enough to shake the eyes back and forth, and the other manifestations of REM are just by-products. This idea makes sense of the fact that REM occurs mostly toward the end of the night's sleep, when the fluid behind the eyes would be the most stagnant. It also fits with the fact that individuals who spend more hours asleep devote a greater percentage of sleep to REM. (If you don't sleep long, you have less need to shake up the stagnant fluid.) People with severe, untreated sleep apnea get less than normal REM sleep, and they do develop abnormalities of the cornea (Chalkiadaki et al., 2021; Gelir et al., 2014).

Stop & Check

20. What kinds of individuals get more REM sleep than others? (Think in terms of age, species, and long versus short sleepers.)

See page 287 for the answer.

Biological Perspectives on Dreaming

Dream research faces a special problem: All we know about dreams comes from people's self-reports. We forget most dreams, and even when we do remember them, the details fade quickly. A common research procedure is to awaken people and ask for an immediate dream report.

The Activation-Synthesis Hypothesis

According to the **activation-synthesis hypothesis**, a dream represents the brain's effort to make sense of sparse and distorted information. Dreams begin with periodic bursts of spontaneous activity in the pons—the PGO waves previously described—that activate parts of the cortex. The cortex combines this haphazard input with whatever other activity was already occurring and does its

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best to synthesize a story that makes sense of the information (Hobson and McCarley, 1977; Hobson et al., 2000; McCarley and Hoffman, 1981).

Consider how this theory handles a couple of common dreams. Most people have occasional dreams of falling or flying. While you are asleep, you lie flat, unlike your posture for the rest of the day. Your brain in its partly aroused condition feels the vestibular sensation of your position and interprets it as flying or falling. Have you ever dreamed that you were trying to move but couldn't? An interpretation based on the activation-synthesis theory is that during REM sleep (which accompanies most dreams), your motor cortex is inactive and your major postural muscles are virtually paralyzed. When you are dreaming, you really *cannot* move, you feel your lack of movement, and you dream of inability to move.

One criticism is that the theory's predictions are vague. If we dream about falling because of the vestibular sensations from lying down, why don't we *always* dream of falling? If we dream that we cannot move because our muscles are paralyzed during REM sleep, why don't we *always* dream of being paralyzed? The main objection is that most dreams have no apparent connection to any current stimuli (Foulkes and Domhoff, 2014; Nir and Tononi, 2010).

The Neurocognitive Model

The **neurocognitive model** regards dreams as thinking that takes place under unusual conditions. It emphasizes that dreams begin with spontaneous brain activity related to recent memories—just as most daytime thinking relates to recent memories (Domhoff, 2011; Solms, 1997, 2000).

Researchers used a PET scan to determine which brain areas increased or decreased their activity during REM, which is correlated with dreaming. Although the research might sound simple, PET requires injecting a radioactive chemical. Imagine trying to give sleepers an injection without awakening them. Further, a PET scan yields a clear image only if the head remains motionless during data collection. If the person tosses or turns even slightly, the blurry image is worthless.

To overcome these difficulties, researchers in two studies persuaded young people to sleep with their heads firmly attached to masks that did not permit any movement. They also inserted a cannula (plastic tube) into each person's arm so that they could inject radioactive chemicals during the night. Imagine yourself in that setup. You have a cannula in your arm and your head is locked into position. Now try to sleep.

Because the researchers foresaw the difficulty of sleeping under these conditions (!), they had their participants stay awake the entire previous night. Someone who is tired enough can sleep even under trying circumstances … maybe.

Now that you appreciate the heroic nature of the procedures, here are the results: During REM sleep, activity increased in the pons (which triggers the onset of REM sleep) and in the hypothalamus, amygdala, and other areas important for emotions and motivations. Activity decreased in the primary visual cortex, the motor cortex, and the dorsolateral prefrontal cortex, but it increased in parts of the parietal and temporal cortex (Braun et al., 1998; Maquet et al., 1996).

The upshot of all this is that the dreaming brain has little sensory input, leaving other brain areas free to generate images without constraints or interference. Because the primary motor cortex is suppressed and the motor areas of the spinal cord are inhibited, arousal cannot lead to action. Activity is suppressed in the prefrontal cortex, which is important for working memory and logical thinking. Consequently, you not only forget most dreams after you awaken, but you also lose track of what has been happening within a dream, and sudden scene changes are common. Remembering your dreams is not very useful (unless you plan to talk about them with your psychoanalyst), because you should not confuse dreams with reality. You also lose a sense of volition—that is, planning (Hobson, 2009). It seems that events just happen, without any intention or planning.

Meanwhile, activity is relatively high in part of the parietal cortex important for visuospatial perception. Patients with damage here report no dreams. Fairly high activity is also found in the areas of visual cortex other than the primary visual cortex. Those areas are presumably important for the visual imagery that accompanies most dreams.

People dream of faces when they have increased activity in the right fusiform gyrus. Dreams about specific locations pair with activity in the posterior parietal cortex. Dreams of moving associate with activity in the right superior temporal sulcus, and dreams of speaking associate with activity in the left temporal lobe (Siclari et al., 2017).

When people are awakened and asked about their dreams, they sometimes reply that they were dreaming, but they do not remember any content. For years these reports were dismissed as forgetting, but a later view is that they were in fact dreams without content, "white dreams," and we have an explanation (Fazekas et al., 2019). If you awaken someone who reports a dream with memorable content, you can detect high activity in that person's posterior parietal cortex. If the person says, "I wasn't dreaming," activity is low in the posterior parietal cortex. When the person reports a white dream with no content, activity is at an intermediate level (Fazekas et al., 2019; Siclari et al., 2017).

The idea behind the neurocognitive approach is that arousal of parts of the cerebral cortex develops into a hallucinatory perception, with no sensory input to override it. This idea, like the activation-synthesis hypothesis, is limited by its lack of specific predictions about who will have what dream and when.

Stop & Check

21. According to the neurocognitive model, why do we have visual imagery during dreams? Why do dreams sometimes make an incoherent or illogical story?

See page 287 for the answer.

Module 8.3 | In Closing

Our Limited Self-Understanding

Without minimizing how much we do understand about sleep, it is noteworthy how many basic questions remain unanswered. What are the functions of REM sleep? Is dreaming useful, or is it just an accident? Our lack of knowledge about activities that occupy so much of our time underscores a point about the biology of behavior: We evolved tendencies to behave in certain ways that lead to survival and reproduction. A behavior can serve its function even when we do not fully understand that function.

Summary

1. One important function of sleep is to conserve energy at times when the individual would be less efficient. Animal species vary in their sleep per day depending on their feeding habits and how much danger they face while asleep. **281**
2. In addition to saving energy, sleep serves other functions, including enhancement of memory. **284**
3. REM sleep occupies the greatest percentage of sleep in the individuals and species that sleep the most total hours. **284**
4. According to the activation-synthesis hypothesis, dreams are the brain's attempts to make sense of the information reaching it, based mostly on haphazard input originating in the pons. **285**
5. REM sleep is associated with activity in several brain areas, including the pons, limbic system, and parts of the parietal and temporal cortex. Activity decreases in the prefrontal cortex, the motor cortex, and the primary visual cortex. **286**
6. According to the neurocognitive hypothesis, dreams originate from the brain's own motivations, memories, and arousal. The stimulation often produces peculiar results because it does not have to compete with normal visual input and does not get organized by the prefrontal cortex. **286**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

activation-synthesis hypothesis **285**
neurocognitive model **286**

Thought Question

Why would it be harder to deprive someone of just NREM sleep than just REM sleep?

Stop & Check Answers

17. The deep ocean, like a cave, has no light and no difference between day and night. These fish might not need to sleep because they are equally efficient at all times of day and have no reason to conserve energy at one time more than another. If they do sleep, they might not follow a circadian rhythm. (Studying deep sea fish is not easy.)

18. Predators get much sleep, and so do species that are unlikely to be attacked during their sleep (such as armadillos).

19. Hippocampal activity repeats experiences of the day, strengthening those memories. The brain deletes the less effective synapses, enabling the ones important for new memories to stand out by contrast.

20. Much REM sleep is more typical of the young than the old, and typical of animals that get much sleep.

21. We have visual imagery because areas of the visual cortex other than the primary visual cortex become active, without any input from the eyes. Dreams are sometimes incoherent or illogical because low activity in the prefrontal cortex means poor memory for what just happened.

Module 8.3 | End-of-Module Quiz

1. What happens to people's body temperature during sleep?
   - **a.** It increases by 1 or 2 degrees.
   - **b.** It remains constant.
   - **c.** It fluctuates rapidly.
   - **d.** It decreases by 1 or 2 degrees.

2. How do whales and dolphins get oxygen at night?
   - **a.** They absorb oxygen from the water.
   - **b.** They sleep in just one hemisphere at a time.
   - **c.** They lower their metabolism so that they need to breathe only a few times per night.
   - **d.** They store oxygen in their digestive system.

3. When frigate birds spend weeks at sea, what do they do about sleep?

a. They sleep while floating on the water.
b. They sleep only in brief episodes, and not much overall.
c. They go without sleep altogether.
d. They sleep as much as usual, but while gliding.

4. If we want to predict how many hours a day some species sleeps, what question would be most helpful in making that prediction?

a. What is the animal's average lifespan?
b. Does the animal live near or far from the equator?
c. Is the animal predator or prey?
d. How intelligent is the animal?

5. How does sleep improve memory?

a. Synapses increase their supply of serotonin and dopamine.
b. Less effective synapses are removed.
c. Overall brain activity increases.
d. The ratio of sodium ions to potassium ions increases.

6. In general, what is true of individuals that get more than an average amount of sleep?

a. Faster than usual cycles through the stages of sleep
b. A higher than average percentage of NREM sleep
c. A higher than average percentage of stage 2 sleep
d. A higher than average percentage of REM sleep

7. How does the neurocognitive hypothesis describe dreams?

a. Disguised representations of unconscious wishes.
b. Reactions to whatever sensory stimuli are present at the time.
c. Memories of the experiences of our ancestors.
d. Thinking that occurs under unusual conditions.

Answers: 1d, 2b, 3b, 4c, 5b, 6d, 7d.

Suggestions for Further Reading

Dement, W. C. (1992). *The sleepwatchers*. Stanford, CA: Stanford Alumni Association.

Fascinating, entertaining account of sleep research by one of its leading pioneers.

Moorcroft, W. H. (2013). *Understanding sleep and dreaming* (2nd ed.). New York: Springer.

Excellent review of the psychology and neurology of sleep and dreams.

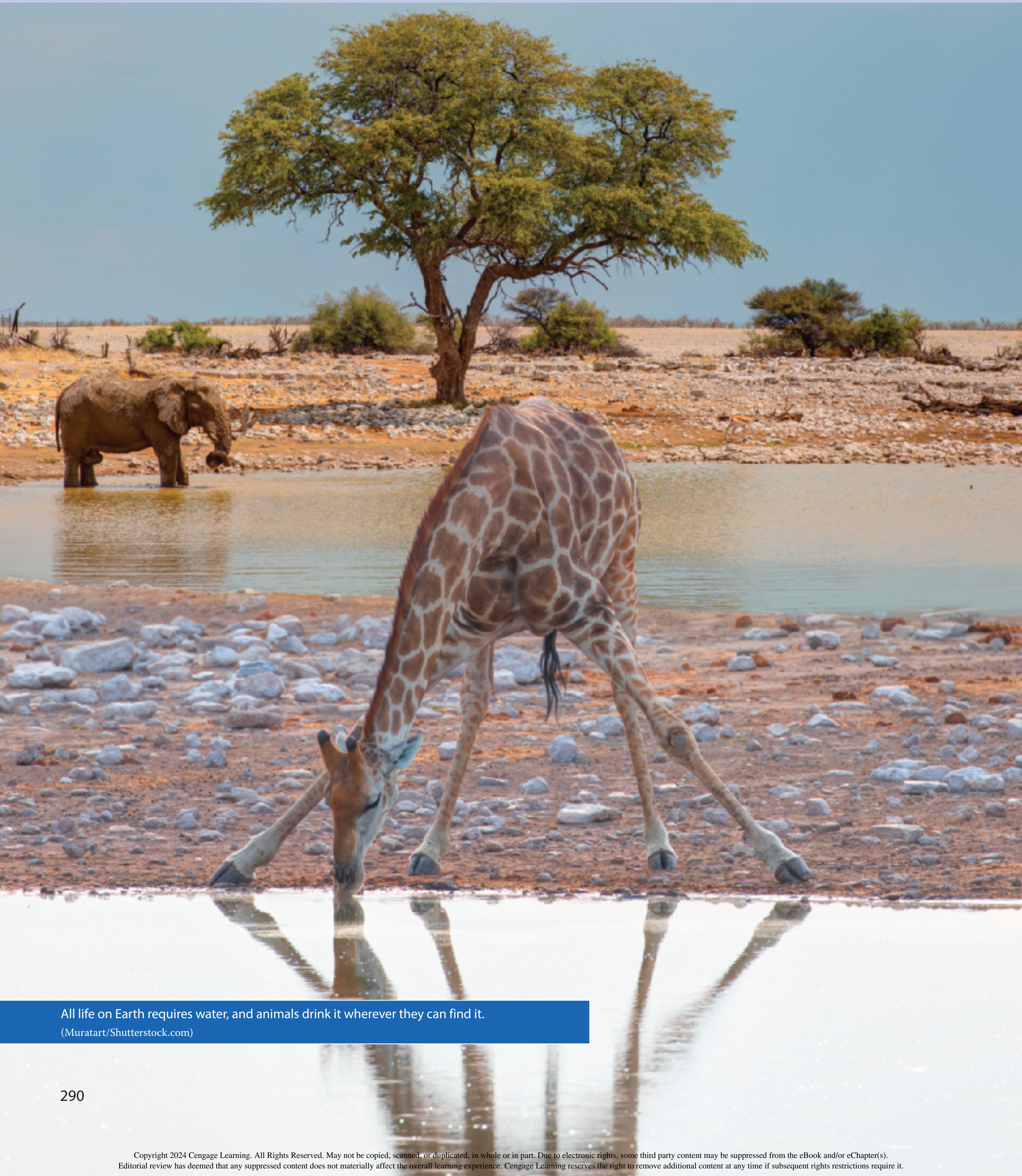
Poe, G. R. (2021). TEDTalk: *The brain science of sleep and why we dream*. https://youtu.be/gofdPqEYZso

A TED Talk by a prominent sleep researcher.

Refinetti, R. (2016). *Circadian physiology* (3rd ed.). Boca Raton, FL: CRC Press.

Marvelous summary of research on circadian rhythms and the relevance to human behavior.

Chapter 9



All life on Earth requires water, and animals drink it wherever they can find it.

(Muratart/Shutterstock.com)

Internal Regulation

Chapter Outline

Module 9.1

Temperature Regulation

Homeostasis and Allostasis
Controlling Body Temperature
In Closing: Combining Physiological and Behavioral Mechanisms

Module 9.2

Thirst

Strategies of Water Regulation
Osmotic Thirst
Hypovolemic Thirst and Sodium-Specific Hunger
In Closing: The Psychology and Biology of Thirst

Module 9.3

Hunger

Digestion and Food Selection
Short- and Long-Term Regulation of Feeding
Brain Mechanisms
Eating Disorders
In Closing: The Multiple Controls of Hunger

Learning Objectives

After studying this chapter, you should be able to:

1. List examples of how temperature regulation contributes to behaviors.
2. Define homeostasis and allostasis.
3. Explain why a constant high body temperature is worth all the energy it costs.
4. Describe the brain mechanisms of temperature control.
5. Discuss why a moderate fever is advantageous in fighting an infection.
6. Distinguish between osmotic and hypovolemic thirst, including the brain mechanisms for each.
7. Discuss sodium-specific hunger.
8. Explain the genetic influences on consumption of dairy products.
9. Discuss influences on food selection.
10. Describe the physiological factors that influence short-term and long-term hunger and satiety.
11. Describe the brain mechanisms of feeding.
12. Discuss common eating disorders.

What is life? You could define life in many ways depending on whether your purpose is medical, legal, philosophical, or poetic. Biologically, the necessary condition for life is *a coordinated set of chemical reactions*. Not all chemical reactions are alive, but all life has well-regulated chemical reactions.

Every chemical reaction in a living body takes place in a water solution at a rate that depends on the types of molecules, their concentration, and their temperature. This chapter is about the behaviors that keep the right chemicals in the right proportions and at the right temperature. It is about the behaviors that keep you alive.

Module 9.1

Temperature Regulation

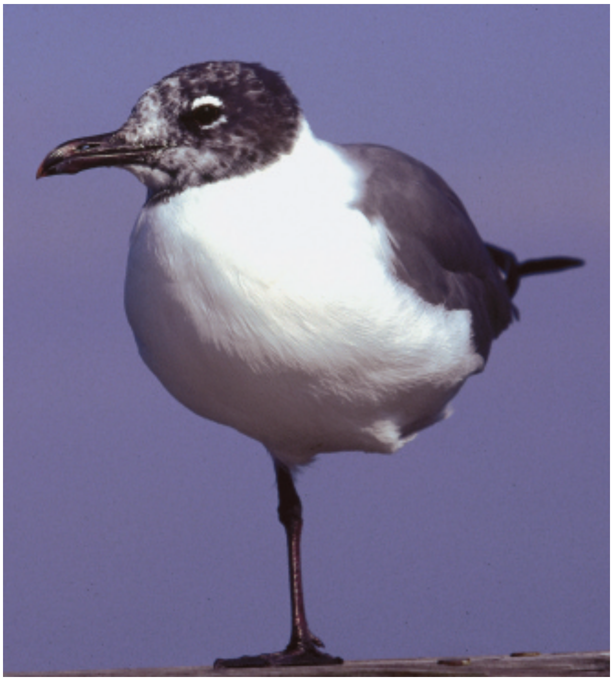
Learning Objectives

After studying this module, you should be able to:

1. List examples of how temperature regulation contributes to behaviors.
2. Define homeostasis and allostasis.
3. Explain why a constant high body temperature is worth all the energy it costs.
4. Describe the brain mechanisms of temperature control.
5. Discuss why a moderate fever is advantageous in fighting an infection.

Figure 9.1 Why do birds sometimes stand on one foot?

Holding a leg next to the body keeps it warm.



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How often have your other psychology courses discussed temperature regulation? Never? Temperature regulation may not sound very psychological, but it has great influences on behavior, in ways that we easily overlook. Here are some behaviors that temperature regulation helps to explain:

- When a small male garter snake emerges from hibernation in early spring, it emits female pheromones for the first day or two. The pheromones attract larger males that swarm all over him, trying to copulate. Presumably, the tendency to release female pheromones must have evolved to provide the small male some advantage. But what? Biologists speculated about ways in which this pseudo-mating experience might help the small male attract real females. The truth is simpler: A small snake that has just emerged from hibernation is so cold that it has trouble slithering out of its burrow. The larger males emerged from hibernation earlier and already had a chance to warm themselves in a sunny place. When the larger males swarm all over the smaller male, they warm him and increase his activity level (Shine et al., 2001).
- Have you ever noticed that large birds sometimes stand on one leg (Figure 9.1)? Why do they do that, when balancing on two legs would seem easier? One reason is to conserve body heat on cold days. By standing on one leg, they protect the heat in the other leg (Ehrlich et al., 1988).
- Vultures sometimes defecate onto their own legs. Are they just careless slobs? No. They defecate onto their legs on hot days so that the evaporating excretions will cool their legs (Ehrlich et al., 1988).
- For many years, biologists puzzled about the function of toucans' huge, clumsy bills (Figure 9.2). One function is temperature regulation (Tattersall et al., 2009). On hot days, a toucan directs more blood flow to the beak, where the passing air cools it, especially while the bird is in flight. At night the toucan tucks its bill under a wing to reduce heat loss.
- Most lizards live solitary lives, but Australian thick-tailed geckos sometimes form tight huddles. Why? They live in an environment with rapid temperature fluctuations. They huddle only when the environmental temperature is falling rapidly. By huddling, they increase insulation and prevent a rapid drop in body temperature (Shah et al., 2003).
- The Japanese giant hornet sometimes invades bee colonies, kills one or more bees, and takes them to feed to its larvae. When one of these hornets invades a hive of Japanese honeybees, the bees form a tight swarm of more than 500, surrounding the hornet in a tiny ball.

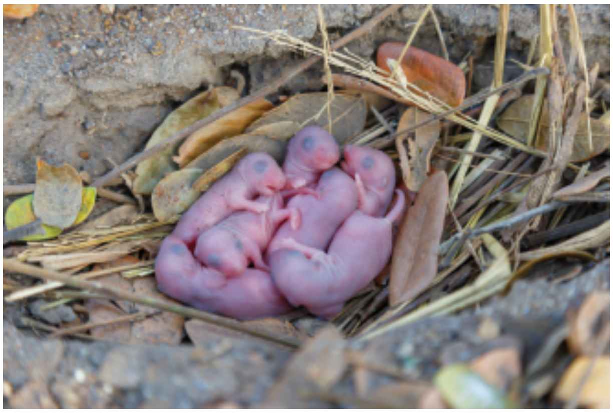
Figure 9.2 Why do toucans have such huge bills?

They use their bills to radiate heat when they need to cool the body. They cover the bill at night.

Hironai/Shutterstock.com

Figure 9.3 Behavior of a newborn rodent depends on temperature

A newborn rat has no hair, thin skin, and little body fat. When exposed to the cold, it becomes inactive.



Prayong k/Shutterstock.com

Why? The combined body heat of all those bees raises the temperature to a level that kills the hornet, but not the bees (Ono et al., 1995).

- Migratory birds do most of their migratory flying at night. The nights are cooler. A bird flying that far in midday would overheat and frequently need to stop for a drink.
- Why do giraffes have such long necks? The traditional assumption is that the long necks enable giraffes to eat leaves from higher in the trees, but a second advantage is important in their tropical environment: A long neck and long legs increase the surface that a giraffe can expose to the air when it needs to cool itself (Mitchell et al., 2017). Also, on hot days a giraffe turns to face the sun, exposing as little as possible of its thin body to direct sun exposure.
- Decades ago, psychologists reported that infant rats appeared deficient in certain aspects of learning, eating, and drinking, until they reached a certain age. Later results showed that the real problem was temperature control. Researchers had been testing the animals at room temperature, about 20° to 23°C (68 to 73°F), which is comfortable for adult humans but dangerously cold for an isolated baby rat (Figure 9.3). Infant rats that seem incapable of a task in a cold room do much better in a warmer room (Satinoff, 1991).
- In some studies female rats learned best during their fertile period (estrus), but in other studies, they learned best a day or two before their fertile period (proestrus). The different results depended on the temperatures of the laboratories. Rats in estrus do better in a cooler environment, presumably because they are generating so much heat on their own. Rats in proestrus do better in a warmer environment (Rubinow et al., 2004).

The point is that we easily overlook the ways in which temperature affects behavior. The modules on thirst and hunger, later in this chapter, present additional examples of how temperature affects behavior.

Homeostasis and Allostasis

Physiologist Walter B. Cannon (1929) introduced the term **homeostasis** (HO-mee-oh-STAY-sis) to refer to biological processes that keep body variables within a fixed range. Homeostasis resembles a house with heating and cooling systems. When the temperature drops below the minimum, the thermostat triggers the furnace to provide heat. When the temperature rises above the maximum, the thermostat turns on the air conditioner. For another example, stand and balance on one foot. Whenever your weight shifts, you correct your position to maintain balance.

Homeostatic processes in animals trigger physiological and behavioral activities that keep variables within a set range. Sometimes the range is so narrow that we call it a **set point**, a single value that the body works to maintain. For example, if calcium is deficient in your diet and its concentration in the blood begins to fall below 0.16 g/L (grams per liter), storage deposits in your bones release additional calcium into the blood. If the calcium level in the blood rises above 0.16 g/L, you store part of the excess in your bones and excrete the rest. Similar mechanisms maintain constant blood levels of water, oxygen, glucose, sodium chloride, protein, fat, and acidity (Cannon, 1929). Actions that reduce discrepancies from the set point produce **negative feedback**. Much of motivated behavior can be described as negative feedback: Something causes a disturbance, and behavior proceeds until it relieves the disturbance.

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However, the body does not maintain complete constancy. Your body temperature is about half a Celsius degree higher in mid-afternoon than in the middle of the night. Hummingbirds let their body temperature fall even further at night, sometimes until the body almost freezes (Shankar et al., 2022). (A tiny bird cannot store enough energy to maintain normal metabolism all night.) Many animals add body fat in fall to prepare for food shortage during the winter. The extra fat also provides insulation against the cold.

Much of our behavior anticipates a need before it occurs. Any sign of danger prompts an increase in heart rate, blood pressure, and sweating, preparing the body for vigorous activity. When the air starts to warm up, a hiker increases thirst and decreases urine production by the kidneys, anticipating probable sweating and dehydration. To describe these dynamic changes, researchers use the term **allostasis** (from the Greek roots meaning "variable" and "standing"), which means the way in which the body anticipates needs, avoiding errors rather than correcting them (McEwen, 2000; Sterling, 2012). Homeostasis and allostasis don't work perfectly, of course. If they did, we would not have problems such as obesity, high blood pressure, or diabetes.

Stop & Check

1. How does allostasis differ from homeostasis?

See page 298 for the answer.

Controlling Body Temperature

If you were to list your strongest motivations in life, you might not think to include temperature regulation, but it has a high priority biologically. An average young adult expends about 2,600 kilocalories (kcal) per day. Where do you suppose all that energy goes? Most of it goes to **basal metabolism**, the energy used to maintain a constant body temperature while at rest. For most people, maintaining body temperature uses about twice as much energy as all the muscle activity, brain activity, and everything else *combined* (Burton, 1994). We produce that much heat largely by metabolism in brown adipose cells, cells that are more like muscle cells than like white fat cells. They burn fuel the way muscle cells do, but they release it as heat instead of as muscle contractions.

Amphibians, reptiles, and most fish are **ectothermic**, meaning that they depend on external sources for body heat instead of generating it themselves. A synonym is *poikilothermic,* from Greek roots meaning "varied heat." An ectothermic animal's body temperature is nearly the same as the temperature of its environment. People often call such animals "cold-blooded," but they are cold only when the environment is cold. Ectothermic animals lack physiological mechanisms of temperature regulation such as shivering and sweating, but they regulate their body temperature behaviorally. A desert lizard moves between sunny areas, shady areas, and burrows to keep body temperature almost constant. However, behavioral methods do not achieve the same degree of constancy that mammals and birds have.

Not all fish, amphibians, and reptiles are completely ectothermic. A few large fish, including sharks and tuna, maintain their core body temperature well above that of the surrounding water most of the time (Bernal et al., 2005). The tegu lizards of South America, about the size of a large rabbit, increase their metabolism during the mating season, raising their body temperature to sometimes 10°C above that of the environment (Tattersall et al., 2016).

Mammals and birds are **endothermic**, meaning that they use physiological mechanisms to keep their core temperature nearly constant. A synonym is *homeothermic,* from Greek roots meaning "same heat." Endothermy is costly, especially for small animals. An animal *generates* heat in proportion to its total mass, but it *radiates* heat in proportion to its surface area. Small mammals and birds, like mice and hummingbirds, have a high surface-to-volume ratio and they radiate heat rapidly. They need much fuel each day to maintain their body temperature.

Only one physiological mechanism, evaporation, cools the body in a hot environment. Humans sweat to expose water for evaporation. For species that don't sweat, the alternatives are licking themselves and panting. As water evaporates, it cools the body. However, if the air is humid as well as hot, the moisture does not evaporate. If you sweat faster than you replace the water by drinking, you become dehydrated, and then you stop sweating, despite the risk of overheating (Tokizawa et al., 2010). People engaged in physical exertion in a hot environment—such as firefighters, soldiers, and farmers—overheat beyond what they can combat by sweating. They risk dehydration, a dangerously high body temperature, heat exhaustion, and organ damage (Pennisi, 2020).

Several physiological mechanisms increase your body heat in a cold environment. One is muscle activity, including shivering. Any muscle contractions, such as those of shivering, generate heat. Second, decreased blood flow to the skin prevents the blood from cooling too much. The consequence to protect the internal organs but let the skin get cold. A third mechanism works well for most mammals, though not humans: When cold, they fluff out their fur to increase insulation. We humans also fluff out our "fur" by erecting the tiny hairs on our skin—"goose bumps." Our remote ancestors with a full coat of fur evolved that mechanism and we inherited it, though it does us little or no good.

We also use behavioral mechanisms, just as ectothermic animals do. In fact, we prefer to rely on behavior whenever we can. The more we regulate our temperature behaviorally, the less energy we need to spend physiologically

Figure 9.4 One way to cope with the heat

On a hot day, wouldn't you do the same?

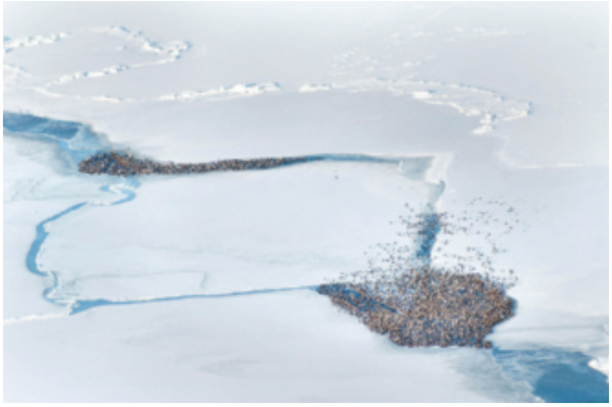
AP Images/Sun-Journal/Ken Love

(Refinetti and Carlisle, 1986). Finding a cool place on a hot day is much better than sweating (Figure 9.4). Finding a warm place on a cold day is much smarter than shivering. Here are a few other behavioral mechanisms of temperature regulation:

- Put on more clothing or take it off. This human strategy accomplishes what other mammals accomplish by fluffing out or sleeking their fur.
- Become more active to get warmer or less active to avoid overheating.
- To get warm, huddle with others. If you are waiting at a bus stop on a cold day and you see someone standing nearby, might you suggest hugging each other to keep warm until the bus arrives? Probably not, but other species have no such inhibitions (Figure 9.5). Emperor penguin chicks huddle together to pool their heat, increasing their insulation enough to survive an Antarctic winter. Spectacled eiders (in the duck family) spend their winters in the Arctic Ocean, which is mostly covered with ice. When more than 150,000 eiders crowd together, they keep warm and melt a hole in the ice where they can dive for fish (Weidensaul, 1999).

Figure 9.5 Behavioral regulation of body temperature

Spectacled eiders pool their body heat to melt holes in the ice of the Arctic Ocean, thereby surviving the winter without migrating.



Aaron Lang/USFWS

Surviving in Extreme Cold

If the atmospheric temperature drops below 0°C (32°F) and you can't find a warmer place, you maintain your body temperature by shivering, shifting blood flow away from the skin, and so forth. An ectothermic animal, which necessarily takes the temperature of its environment, is vulnerable. If its body temperature drops below the freezing point of water, ice crystals form. Because water expands when it freezes, ice crystals would tear apart blood vessels and cell membranes, killing the animal.

Many amphibians and reptiles avoid that risk by burrowing or finding other sheltered locations. However, some frogs, fish, and insects survive through winters in northern Canada where even the underground temperature approaches −40°C (which is also −40°F). How do they do it? Some insects and fish stock their blood with glycerol and other antifreeze chemicals at the start of the winter (Liou et al., 2000). Wood frogs in Canada and Alaska actually do freeze, but they have mechanisms to reduce the damage. They start by withdrawing most fluid from their organs and blood vessels and storing it in extracellular spaces. Therefore, ice crystals have room to expand when they form, without tearing blood vessels or cells. Also, the frogs have chemicals that cause ice crystals to form gradually, not in chunks. Finally, they have extraordinary blood-clotting capacity that quickly repairs any blood vessels that do rupture (Storey and Storey, 1999).

The Advantages of Endothermy

As mentioned, we spend about two-thirds of our total energy maintaining body temperature (basal metabolism). If we didn't maintain a constant, high body temperature, we could eat less and spend less effort finding food. Maintaining body temperature must provide an important advantage, or we would not have evolved these energy-expensive mechanisms. What is that advantage?

Think back to the chapter on movement: As the water gets colder, a fish recruits more and more fast-twitch muscle fibers to remain active, running the risk of rapid fatigue. The same is true for amphibians and reptiles. On a very cold day, a lizard has to change its defense strategy: If it ran away from a predator, it would either run more slowly than usual or fatigue rapidly. So, instead of running, it tries to fight the predator—an act requiring a briefer burst of activity, and often a losing battle (James, 2013).

Birds and mammals keep warm at all times and therefore stay constantly ready for vigorous activity, regardless of the air temperature. In other words, we eat a great deal to support high metabolism so that even if the weather is cold, we can remain highly active without great fatigue. Let's qualify this point just a bit: On a cold day, you divert blood away from the periphery to protect the internal organs and to avoid losing too much heat to the surrounding air. The result is that your muscles are a bit cooler than usual. A competitive athlete needs to warm up, literally, to increase the muscles' temperature on a cold day.

Why did mammals evolve a body temperature of 37°C (98°F) instead of some other value? From the standpoint of vigorous muscle activity, it is best to be as warm as possible. A warmer animal runs faster with less fatigue. When a reptile has a choice of environments at different temperatures, it usually chooses to warm itself to 37° to 38°C (98° to 100°F), about the same temperature as endothermic animals (Wagner and Gleeson, 1997).

If warmer is better, why not heat ourselves even higher? First, maintaining a higher temperature requires more fuel and energy. Second, and more importantly, beyond about 41°C (105°F), most proteins begin to break their bonds and lose their useful properties. Birds' body temperatures are in fact about 41°C. It is possible to evolve proteins that are stable at higher temperatures. Indeed, odd microscopic animals called thermophiles survive in boiling water. However, to do so, they need many extra chemical bonds to stabilize their proteins. The enzymatic properties of a protein depend on its flexibility, so making proteins rigid enough to withstand high temperatures makes them inactive at more moderate temperatures (Feller, 2010). In short, our body temperature of 37°C is a trade-off between the advantages of high temperature for rapid movement and the disadvantages of high temperature for protein stability.

Reproductive cells require a cooler environment than the rest of the body (Rommel et al., 1998). Birds lay eggs and sit on them, instead of developing them internally, because the birds' internal temperature is too hot for an embryo. Similarly, in most male mammals, the scrotum hangs outside the body, because sperm production requires a cooler temperature than the rest of the body. (It's not just for decoration.) A man who wears his undershorts too tight keeps his testes too close to the body, overheats them, and produces fewer healthy sperm cells. Pregnant women are advised to avoid hot baths and anything else that might overheat a developing fetus.

Stop & Check

2. What is the primary advantage of maintaining a constant high body temperature?
3. Why did mammals evolve a temperature of 37°C (98°F) instead of some other temperature?

See page 299 for the answer.

Brain Mechanisms

The physiological changes that regulate body temperature—such as shivering, sweating, and changes in blood flow to the skin—depend on areas in and near the hypothalamus (Figure 9.6). Behavioral methods of temperature regulation, such as finding a cooler or warmer place, also depend on the hypothalamus (Jung et al., 2022). Physiological regulation depends mainly on the anterior hypothalamus and the preoptic area, located just anterior to the anterior hypothalamus. It is called *preoptic* because it is near the optic chiasm, where the optic nerves cross. Because of the close relationship between the preoptic area and the anterior hypothalamus, researchers often treat them as a single area, the **preoptic area/anterior hypothalamus**, or **POA/AH**. The POA/AH and a couple other hypothalamic areas send output to the hindbrain's raphe nucleus, which controls the autonomic responses such as shivering, sweating, changes in heart rate and metabolism, and changes in blood flow to the skin (Morrison, 2016; Yoshida et al., 2009).

The POA/AH receives input from temperature receptors in the skin and organs, and about 30 percent of the neurons in the POA/AH sense changes in their own temperature (Song et al., 2016; Wang et al., 2019). If either the skin or the hypothalamus is hot, an animal sweats or pants vigorously and seeks a cooler location. If either one is cold, the animal shivers and seeks a warmer location. After damage to the POA/AH, mammals regulate body temperature mainly by the behavioral mechanisms that a lizard might use, such as seeking a warmer or colder location (Satinoff and Rutstein, 1970; Van Zoeren and Stricker, 1977).

Stop & Check

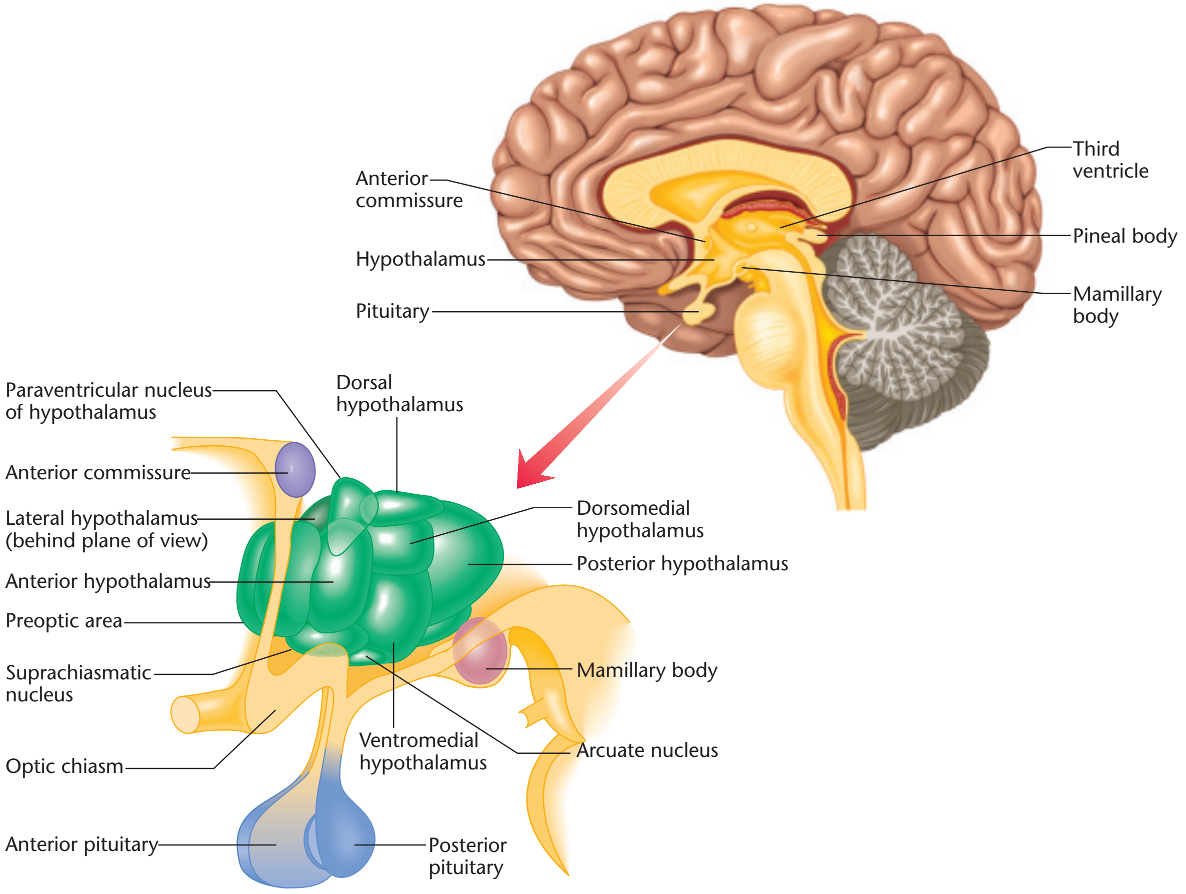
4. What are the sources of input to the POA/AH?
5. If you had damage to your POA/AH, what would happen to your body temperature?

See page 299 for the answer.

Fever

When you have an infection, the immune system reacts by producing prostaglandins and histamines that induce the POA/AH to raise the set point for body temperature. The body reacts by shivering and other processes that produce a fever. (Ek et al., 2001; Leon, 2002; Tabarean et al., 2012). Just as you shiver or sweat when your body temperature goes below or above its usual 37°C, when you have a fever, you shiver or sweat whenever your temperature deviates from the new level. Moving to a cooler room does not lower your fever. Your body just works harder to keep its temperature at the feverish level. In other words, fever is something the hypothalamus directs the body to produce. People lacking the receptors for prostaglandins and histamines fail to develop a fever, even if they have pneumonia

Figure 9.6 Major subdivisions of the hypothalamus and pituitary

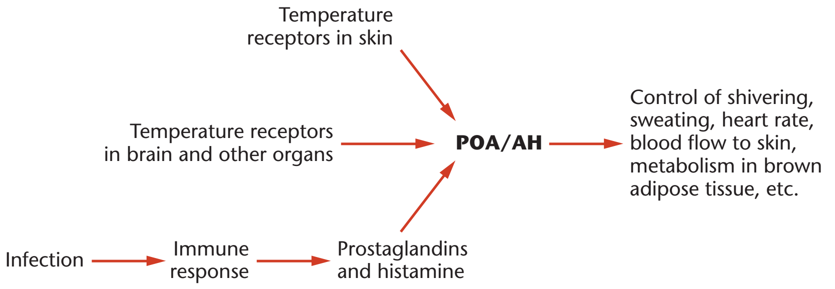

Anterior commissure
Hypothalamus
Pituitary
Third ventricle
Pineal body
Mamillary body
Paraventricular nucleus of hypothalamus
Dorsal hypothalamus
Anterior commissure
Lateral hypothalamus (behind plane of view)
Anterior hypothalamus
Preoptic area
Suprachiasmatic nucleus
Optic chiasm
Anterior pituitary
Dorsomedial hypothalamus
Posterior hypothalamus
Mamillary body
Ventromedial hypothalamus
Arcuate nucleus
Posterior pituitary

(**Source:** Based on Nieuwenhuys et al., 1988)

or similar diseases (Hanada, et al., 2009). Figure 9.7 summarizes all the inputs to the POA/AH.

Because newborn rabbits have an immature hypothalamus, they do not shiver in response to infections. If they are given a choice of environments, however, they select a spot warm enough to raise their body temperature and produce a fever by behavioral means (Satinoff et al., 1976). Fish and reptiles with an infection also choose a warm enough environment, if they can find one, to produce a feverish body temperature (Kluger, 1991). Again, the point is that fever is something the animal does to fight an infection.

Figure 9.7 Integration of temperature information by the POA/AH


Temperature receptors in skin
Temperature receptors in brain and other organs
POA/AH
Control of shivering, sweating, heart rate, blood flow to skin, metabolism in brown adipose tissue, etc.
Infection
Immune response
Prostaglandins and histamine

(**Source:** The POA/AH maintains a set point for body temperature, which can increase to produce a fever.)

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Does fever do any good? Certain types of bacteria grow less vigorously at high temperatures than at normal mammalian body temperatures. Also, the immune system works more vigorously at an increased temperature (Skitzki et al., 2007). Other things being equal, developing a moderate fever increases an individual's chance of surviving a bacterial infection (Kluger, 1991). However, a fever above about 39°C (103°F) in humans does more harm than good, and a fever above 41°C (106°F) is life-threatening (Rommel et al., 1998).

Stop & Check

6. What evidence indicates that fever is an adaptation to fight illness?

See page 299 for the answer.

Module 9.1 | In Closing

Combining Physiological and Behavioral Mechanisms

Physiological mechanisms and behavioral mechanisms work together. Your body has physiological mechanisms to maintain constant body temperature, including shivering, sweating, and changes in blood flow, but you also rely on behavioral mechanisms, such as finding a cooler or warmer place, changing clothing, and so forth. Redundancy reduces your risk: If one mechanism fails, another mechanism comes to your rescue. We shall see this theme again in the discussions of thirst and hunger.

Summary

1. It is easy to overlook the importance of temperature regulation. Many seemingly odd animal behaviors make sense as ways to heat or cool the body. **292**
2. Homeostasis is a tendency to maintain a body variable near a set point. Allostasis is an adaptation to prepare for expected changes. **293**
3. All animals use behavioral mechanisms to regulate body temperature whenever possible. Birds and mammals supplement with physiological mechanisms to maintain a constant elevated temperature. **294**
4. A steady high temperature enables a mammal or bird to move rapidly without excessive fatigue even in a cold environment. **295**
5. From the standpoint of muscle activity, higher body temperature is better. However, as temperatures increase, protein stability decreases, and more energy is needed to maintain body temperature. Mammalian body temperature of 37°C is a compromise between these competing considerations. **296**
6. The preoptic area and anterior hypothalamus (POA/AH) are critical for temperature control. Cells there monitor both their own temperature and that of the skin and organs. When they receive input indicating an infection, they initiate responses that produce a fever. **296**
7. A moderate fever helps an animal combat an infection. **297**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

allostasis	**294**
basal metabolism	**294**
ectothermic	**294**
endothermic	**294**
homeostasis	**293**
negative feedback	**293**
preoptic area/anterior hypothalamus POA/AH	**296**
set point	**293**

Thought Question

Speculate on why birds have higher body temperatures than mammals.

Stop & Check Answers

1. Homeostasis keeps certain body variables within a fixed range by reacting to changes. Allostasis acts in advance to prevent or minimize changes.
2. A constant high body temperature keeps an animal ready for rapid, prolonged muscle activity even in cold weather.

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3. Animals gain an advantage in being as warm as possible and therefore as fast as possible. However, proteins lose stability at still higher temperatures.
4. The POA/AH receives input from temperatures in the skin and organs, and many cells sense their own temperature.
5. You would be much less able to shiver, sweat, or control other physiological mechanisms that control body temperature. However, you could still try to find a place in the environment that keeps you close to your normal temperature.
6. During a fever, the body will shiver or sweat to maintain its elevated temperature at a nearly constant level. Also, fish, reptiles, and immature mammals with infections use behavioral means to raise their temperature to a feverish level. Furthermore, a moderate fever inhibits bacterial growth and increases the probability of surviving a bacterial infection.

Module 9.1 | End-of-Module Quiz

1. What is allostasis?
   - **a.** Processes that react to any change to bring the body back to equilibrium
   - **b.** Processes that anticipate future needs
   - **c.** Random changes in the internal processes of the body
   - **d.** The ideal levels of all body variables

2. For most people, maintaining constant body temperature requires how much of the body's total energy output?
   - **a.** One or two percent
   - **b.** About one-tenth
   - **c.** About one-third
   - **d.** About two-thirds

3. How do reptiles and amphibians regulate their body temperature, if at all?
   - **a.** They move to a location with a more favorable temperature.
   - **b.** They use physiological mechanisms such as shivering and sweating.
   - **c.** They increase their metabolic rate.
   - **d.** They do not regulate their body temperature at all.

4. What is the primary advantage of maintaining a constant high body temperature?
   - **a.** It saves us the energy from having to look for a comfortable temperature.
   - **b.** It keeps the muscles ready for rapid, prolonged activity even in cold weather.
   - **c.** It enables the digestive system to process a greater variety of nutrients.
   - **d.** It enables us to survive in warmer climates.

5. Cells in the POA/AH regulate body temperature by monitoring what?
   - **a.** Stomach secretions and muscle activity
   - **b.** Blood volume and the salt concentration in the blood
   - **c.** Skin temperature and the sugar concentration in the blood
   - **d.** Skin temperature and the temperature of the POA/AH itself

6. When you have an infection, what causes the fever?
   - **a.** The infective agent stimulates the heart to beat faster.
   - **b.** The infective agent impairs the activity of the hypothalamus.
   - **c.** The immune system delivers chemicals that stimulate the hypothalamus.
   - **d.** The immune system decreases blood flow to the brain.

7. Why is a very high body temperature dangerous?
   - **a.** Many proteins break down at high temperatures.
   - **b.** High temperatures interfere with muscle contractions.
   - **c.** High temperatures increase the ratio of excitation to inhibition in the brain.
   - **d.** High temperatures stimulate excessive eating and drinking.

Answers: 1b, 2d, 3a, 4b, 5d, 6c, 7a.

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Module 9.2

Thirst

Learning Objectives

After studying this module, you should be able to:

6. Distinguish between osmotic and hypovolemic thirst, including the brain mechanisms for each.
7. Discuss sodium-specific hunger.

Water constitutes about 70 percent of your body. Because the concentration of chemicals in water determines the rate of chemical reactions, you need to maintain the water in your body within narrow limits. You also need enough fluid in the circulatory system to maintain normal blood pressure. You could survive for days, maybe weeks without food, but not long without water. When you need water, axons from the hypothalamus modify the responses of more than half the cells in the cortex to increase their responses to any signal of water availability (Allen et al., 2019). That is, when you are thirsty, most of your brain is preoccupied with satisfying that need.

Strategies of Water Regulation

Species differ in their strategies for maintaining water. Beavers and other animals that live in rivers or lakes drink plenty of water, eat moist foods, and excrete dilute urine. Gerbils and other desert animals can go through life without drinking at all. They gain water from their food, and they retain water by excreting dry feces and concentrated urine. Unable to sweat, they avoid the heat of the day by burrowing under the ground. Their convoluted nasal passages minimize water loss when they exhale. Yellowbellied sea snakes of the Indian and Pacific oceans require fresh water to survive. They get it by drinking rainwater that falls at the top of the ocean during the rainy season, and then they conserve that water during the dry season that can last more than half a year (Lillywhite et al., 2019).

We humans vary our strategy depending on circumstances. If you cannot find enough to drink or if the water tastes bad, you conserve water by excreting more concentrated urine and decreasing your sweat, somewhat like a gerbil, although not to the same extreme. Your posterior pituitary (Figure 9.6) releases the hormone **vasopressin** that raises blood pressure by constricting blood vessels. (The term *vasopressin* comes from *vas*cular *press*ure.) The increased pressure helps compensate for the decreased blood volume. Vasopressin is also known as **antidiuretic hormone (ADH)** because it enables the kidneys to reabsorb water from urine and make the urine more concentrated. (*Diuresis* means "urination.")

When water is available, our strategy is closer to that of beavers: We drink more than we need and excrete the excess. (However, if you drink extensively without eating, as many alcoholics do, you may excrete enough body salts to harm yourself.) Most of our drinking is with meals or in social situations, and most people in prosperous countries seldom experience intense thirst.

Stop & Check

7. If you lacked vasopressin, would you drink more like a beaver or like a gerbil? Why?

See page 303 for the answer.

Osmotic Thirst

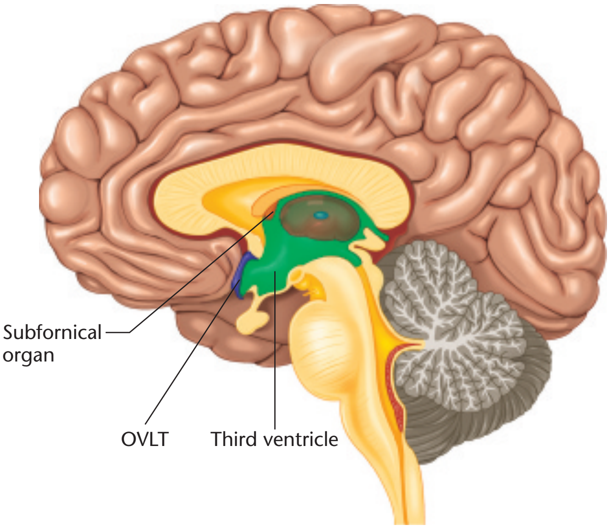
We distinguish two types of thirst. Eating salty foods causes *osmotic* thirst. Losing fluid by bleeding or sweating induces *hypovolemic* thirst.

The combined concentration of all solutes in mammalian body fluids remains at a nearly constant level of 0.15 M (molar). Molarity is a measure of the number of particles per unit of solution. (A 1.0 M solution of sugar and a 1.0 M solution of sodium chloride have the same number of molecules per liter.) This fixed concentration of solutes is a set point, like the set point for temperature. Any deviation activates mechanisms that restore the concentration of solutes to the set point.

Osmotic pressure is the tendency of water to flow across a semipermeable membrane from an area of low solute concentration to an area of higher concentration. A semipermeable membrane is one through which water can pass but solutes cannot. The membrane surrounding a cell is almost a semipermeable membrane, because water flows across it freely and various solutes flow either slowly or not at all. If you eat something salty, sodium ions accumulate in the extracellular fluid. The result is a higher concentration of solutes outside the cells than inside, and the resulting osmotic pressure draws water from the cells into the extracellular fluid.

Figure 9.8 The brain's receptors for osmotic pressure and blood volume

These neurons are in areas surrounding the third ventricle of the brain.



(**Source:** Based in part on DeArmond et al., 1974; Weindl, 1973)

Receptors in areas around the third ventricle, including the **OVLT** (organum vasculosum laminae terminalis) and the **subfornical organ (SFO)** (Hiyama et al., 2004) (Figure 9.8) detect osmotic pressure and the sodium content of the blood (Tiruneh et al., 2013). When these neurons detect increased osmotic pressure by noting their own loss of water, they trigger **osmotic thirst**, a drive for water that helps restore the normal state (Figure 9.9).

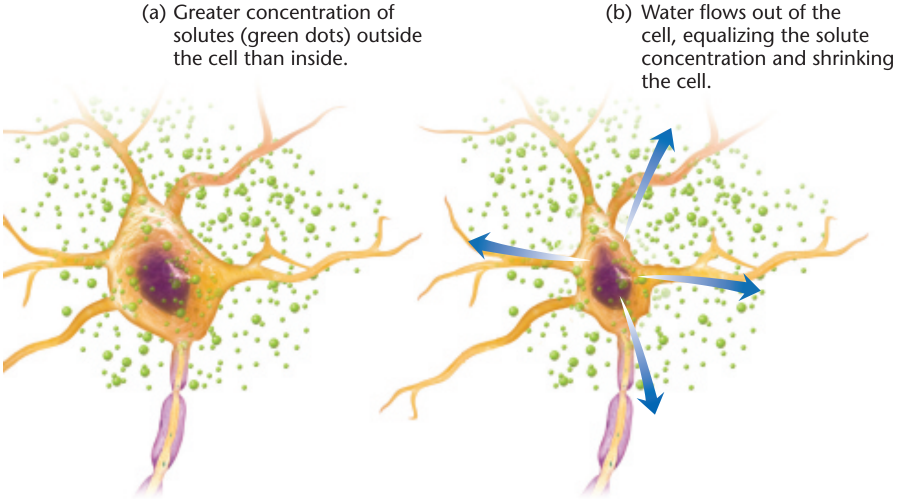
Axons from the OVLT and SFO combine with input from the stomach and elsewhere to provide input to the hypothalamus. In reaction to osmotic thirst, the **lateral preoptic area** and surrounding parts of the hypothalamus increase drinking (Saad et al., 1996), while the **supraoptic nucleus** and **paraventricular nucleus (PVN)** stimulate the posterior pituitary to release vasopressin.

Shortly before time to go to sleep, the body's circadian rhythm triggers increased secretion of vasopressin (Gizowki et al., 2016; Trudel and Bourque, 2010). As a result, you feel an urge to drink something, even if your cells' osmotic pressure is normal at the time. The vasopressin also inhibits your need to urinate and therefore enables you to get through the night without becoming dehydrated.

After you eat or drink, changes in blood osmotic pressure take time, but you adjust your thirst long before that takes place. When you eat a meal, especially a salty meal, you drink at once instead of waiting until your osmotic pressure changes. The OVLT receives input from receptors in the digestive tract that inform about the food, water, and salt content, enabling it to anticipate the osmotic need (Bourque, 2008; Zimmerman et al., 2019). The OVLT also receives input from the tongue, and each lick of water decreases thirst by a tiny amount, long before the blood could distribute the water to reduce osmotic pressure (Zimmerman, 2020). When food or water reaches the intestines, it passes through the liver before entering the general circulation. Receptors in the circulation to the liver detect the osmotic concentration of the fluid, and if it is low, they signal the brain to decrease thirst (Ichiki et al., 2022). Still, although all this is good, the process is imperfect. Severely dehydrated people stop drinking before they have satisfied their need (Pennisi, 2020).

Figure 9.9 The consequence of a difference in osmotic pressure

(a) Suppose a solute such as NaCl is more concentrated outside the cell than inside. **(b)** Water flows by osmosis out of the cell until the concentrations are equal. Neurons in certain brain areas detect their own dehydration and trigger thirst.


(a) Greater concentration of solutes (green dots) outside the cell than inside.
(b) Water flows out of the cell, equalizing the solute concentration and shrinking the cell.

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Stop & Check

8. Would adding salt to the body's extracellular fluids increase or decrease osmotic thirst?
9. Why are you likely to feel thirst just before bedtime? Would you feel just as thirsty if you went to sleep at an unusual time?

See page 303 for the answer.

Hypovolemic Thirst and Sodium-Specific Hunger

If you lose a significant amount of body fluid by bleeding, diarrhea, or sweating, your body's osmotic pressure stays the same, but you need fluid. Receptors in your kidneys and on your blood vessels react to the decreased blood pressure by sending messages to the OVLT and the SFO—the same areas that respond to osmotic thirst. Those areas have some cells that detect osmotic pressure, some that respond to blood volume, and a few that are sensitive to both (Pool et al., 2020). The cells detecting low blood pressure prompt the posterior pituitary gland to release vasopressin, which constricts blood vessels. Also, the kidneys release the enzyme *renin,* which sets off a series of reactions to produce **angiotensin II**. Like vasopressin, angiotensin II constricts the blood vessels, compensating for the drop in blood pressure (Figure 9.10).

Angiotensin II also triggers thirst, in conjunction with receptors that detect blood pressure in the large veins. However, thirst caused by low blood volume, known as **hypovolemic** (HI-po-vo-LEE-mik) **thirst**, differs from osmotic thirst, because you need to restore lost salts and not just water. When angiotensin II reaches the brain, it stimulates neurons that release angiotensin II as a neuromodulator (Tanaka et al., 2001). That is, neurons regulating hypovolemic thirst both respond to angiotensin II and release it.

Whereas an animal with osmotic thirst needs water, one with hypovolemic thirst cannot drink much pure water. Pure water would dilute the body fluids and lower the solute concentration in the blood. The animal therefore increases its preference for salty water (Stricker, 1969).

Deficiency in sodium provokes **sodium-specific hunger**, a drive to consume salty tastes (Richter, 1936). You may have noticed this phenomenon yourself. A woman around the time of menstruation, or anyone who has sweated heavily, finds that salty snacks taste especially good. In contrast to this built-in mechanism for salt preference, animals have to learn specific hungers for other vitamins and minerals (Rozin and Kalat, 1971).

Table 9.1 | Osmotic and Hypovolemic Thirst

Type of Thirst	Caused by	Best Relieved by	Receptor Location
Osmotic	High solute concentration outside cells	Pure water	OVLT, subfornical organ, and digestive tract
Hypovolemic	Low blood volume	Water containing solutes	OVLT, subfornical organ, kidneys and blood vessels

Sodium regulation depends on hormones (Schulkin, 1991). When the body's sodium reserves are low, the adrenal glands release the hormone **aldosterone** (al-DOSS-ter-one) that causes the kidneys, salivary glands, and sweat glands to retain salt (Verrey and Beron, 1996). Long ago, a child showed an unusual craving for salt. "Salt" was one of the first words he learned. He demanded a layer of salt on everything he ate, and he ate salt directly from the shaker. At age 3½, he had a hospital stay, where they fed him only the usual amount, and he died of salt deficiency. Autopsy revealed that his adrenal glands were defective, unable to produce aldosterone. Therefore, he was constantly excreting sodium and he needed to ingest it constantly to replenish his supplies (Wilkins and Richter, 1940).

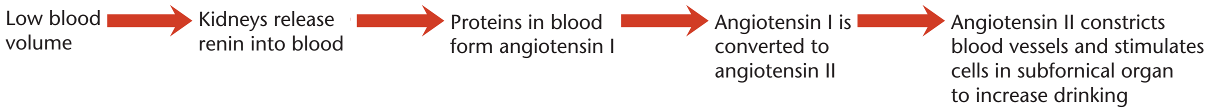
Aldosterone and angiotensin II together stimulate the increase in salt preference (Jarvie and Palmiter, 2017; Krause and Sakal, 2007). Aldosterone indicates low sodium, and angiotensin II indicates low blood volume. Either one by itself produces only a small increase in sodium intake, but their combined effect is substantial, (Geerling and Loewy, 2008). Table 9.1 summarizes the differences between osmotic thirst and hypovolemic thirst.

Stop & Check

10. Who would drink more pure water—someone with osmotic thirst or someone with hypovolemic thirst?
11. What are the contributions of angiotensin II and aldosterone?

See page 303 for the answer.

Figure 9.10 Hormonal response to hypovolemia


Low blood volume
Kidneys release renin into blood
Proteins in blood form angiotensin I
Angiotensin I is converted to angiotensin II
Angiotensin II constricts blood vessels and stimulates cells in subfornical organ to increase drinking

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Module 9.2 | In Closing

The Psychology and Biology of Thirst

You may have thought that temperature regulation happens automatically, and that water regulation depends on your behavior. You can see now that the distinction is not entirely correct. You control your body temperature partly by automatic means, such as sweating or shivering, but also partly by behavioral means, such as choosing a warm or a cool place. You control your body water partly by the behavior of drinking but also by hormones that alter kidney activity. If your kidneys cannot regulate your water and sodium adequately, your brain gets signals to change your drinking or sodium intake. Keeping your body's chemical reactions going depends on both skeletal and autonomic controls.

Summary

1. Animals have evolved ways of maintaining body water, ranging from frequent drinking to extreme conservation of fluids. Humans alter their strategy depending on the availability of acceptable fluids. **300**
2. An increase in the osmotic pressure of the blood draws water out of cells, causing osmotic thirst. Neurons in the OVLT and subfornical organ detect changes in osmotic pressure and send information to hypothalamic areas responsible for vasopressin secretion and for drinking. **300**
3. The circadian rhythm triggers increased vasopressin release just before bedtime, producing increased thirst at the moment and decreased urine production during the night. The result helps you get through the night without either drinking or urinating. **301**
4. The OVLT decreases thirst after drinking, long before the ingested water reaches the cells that need it. **301**
5. Loss of blood volume causes hypovolemic thirst. Satisfying hypovolemic thirst requires water containing solutes. **302**
6. Hypovolemic thirst is triggered by the hormone angiotensin II, which increases when blood pressure falls. **302**
7. Loss of sodium salts from the body triggers a craving for salty tastes. **302**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

aldosterone	**302**
angiotensin II	**302**
antidiuretic hormone (ADH)	**300**
hypovolemic thirst	**302**
lateral preoptic area	**301**
osmotic pressure	**300**
osmotic thirst	**301**
OVLT	**301**
paraventricular nucleus (PVN)	**301**
sodium-specific hunger	**302**
subfornical organ (SFO)	**301**
supraoptic nucleus	**301**
vasopressin	**300**

Thought Questions

1. An injection of concentrated sodium chloride triggers osmotic thirst, but equally concentrated glucose does not. Why not?
2. If all the water you drank leaked out through a tube connected to the stomach, how would your drinking change?
3. Many women crave salt during pregnancy. Why?

Stop & Check Answers

7. If you lacked vasopressin, you would have to drink more like a beaver. You would excrete much fluid, so you would need to drink an equal amount to replace it.
8. Adding salt to the extracellular fluids would increase osmotic thirst because it would draw water from the cells into the extracellular spaces.
9. At bedtime, your body secretes vasopressin, which helps conserve water and also stimulates thirst. Both responses help you get through the night while you cannot drink. Your circadian rhythm triggers the increased vasopressin, so you would not feel as thirsty before sleep at an unusual time.
10. Someone with osmotic thirst would drink more water. Someone with hypovolemic thirst would drink more of a solution containing salts.
11. Angiotensin II constricts the blood vessels, and stimulates neurons that produce hypovolemic thirst. Aldosterone causes the body to retain salt when blood volume is low.

Module 9.2 | End-of-Module Quiz

1. What does vasopressin do?
   - **a.** It stimulates hypovolemic thirst.
   - **b.** It constricts blood vessels.
   - **c.** It increases digestion in the intestines.
   - **d.** It increases the deposit of calcium into the bones.

2. What else does vasopressin do?
   - **a.** It prevents fluctuations of body temperature.
   - **b.** It increases salt appetite.
   - **c.** It makes urine more concentrated.
   - **d.** It increases the flow of glucose into the cells.

3. Which of these happens after you eat something salty?
   - **a.** The sodium-potassium pump becomes less active.
   - **b.** The sodium-potassium pump becomes more active.
   - **c.** Salt flows into the cells.
   - **d.** Water flows out of the cells.

4. What would happen as a result of adding salt to the body's extracellular fluids?
   - **a.** Increased osmotic thirst
   - **b.** Decreased osmotic thirst
   - **c.** Increased hypovolemic thirst
   - **d.** Decreased hypovolemic thirst

5. What do the OVLT and the subfornical organ monitor?
   - **a.** Insulin and glucagon levels
   - **b.** Heart rate and body temperature
   - **c.** Osmotic pressure and blood volume
   - **d.** The balance between excitatory and inhibitory transmission

6. What is the most effective way to satisfy hypovolemic thirst?
   - **a.** Drink pure water slowly.
   - **b.** Drink pure water rapidly.
   - **c.** Drink water containing salt or other solutes.
   - **d.** Alternate between drinking water and drinking alcohol.

7. What does aldosterone do?
   - **a.** It decreases appetite.
   - **b.** It helps the brain store long-term memories.
   - **c.** It helps the kidneys and other glands retain salt.
   - **d.** It helps the suprachiasmatic nucleus control the circadian rhythm.

Answers: 1b, 2c, 3d, 4a, 5c, 6c, 7c.

Module 9.3

Hunger

Learning Objectives

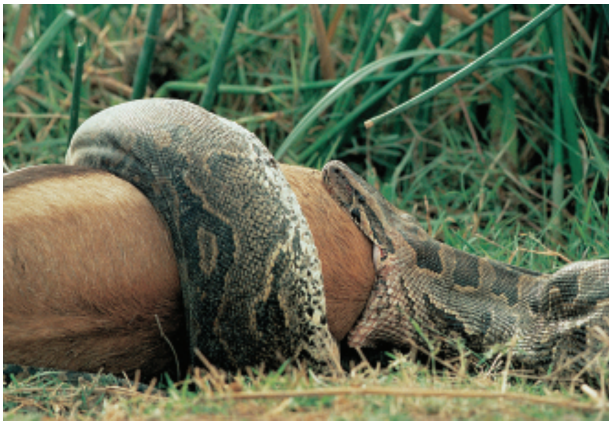
After studying this module, you should be able to:

8. Explain the genetic influences on consumption of dairy products.
9. Discuss influences on food selection.
10. Describe the physiological factors that influence short-term and long-term hunger and satiety.
11. Describe the brain mechanisms of feeding.
12. Discuss common eating disorders.

Species differ in their eating strategies. A snake or crocodile might devour a huge meal and then eat nothing more for months (Figure 9.11). Bears eat as much as they can whenever they can. It is a sensible strategy because bears' main foods—fruits and nuts—are available in large quantities for only short times. Bears' occasional feasts tide them over through times of starvation. You might think of it as survival of the fattest. (Sorry about that one.)

Figure 9.11 A python swallowing a gazelle

The gazelle weighed about 50 percent more than the snake. Many reptiles eat huge but infrequent meals. Their total intake over a year is far less than that of a mammal.


Okapia/Robert Harding

A small bird, at the other extreme, eats only what it needs at the moment. Low weight helps it fly away from predators, and even a few extra milligrams might make a difference (Figure 9.12). However, in cold climates, a bird needs to store a substantial amount to get through the night. To survive through Alaska winters at night, a chickadee finds a hollowed tree or other nesting site that provides as much insulation as possible. Then it lowers its body temperature into a state almost like hibernation. It shivers throughout the night to prevent its body from freezing, and all that shivering requires energy. During Alaskan winters, a chickadee eats enough each day to increase its body weight by 10 percent and then loses that amount at night (Harrison, 2008; Sharbaugh, 2001). For comparison, imagine a 50 kg (110 lb) person gaining 5 kg (11 lb) during the day and then shivering it off at night.

Figure 9.12 A great tit, a small European bird

Ordinarily, when food is abundant, tits eat just what they need each day and maintain minimal fat reserves. When food is harder to find, they eat more and live off fat reserves between meals. During an era when their predators were scarce, they started putting on more fat.

Arco Images/Rolfes, W./Arco Images GmbH/Alamy Stock Photo

Human eating is noteworthy in that we have a relatively small digestive system for an animal of our size. A prominent speculation is that our ability to cook food and make it easier to digest enabled us to evolve a smaller digestive system and nevertheless gain all the energy we need for a large brain.

Choosing which food to eat and how much to eat is an important decision. We use a wide array of learned and unlearned mechanisms to help in the process.

Digestion and Food Selection

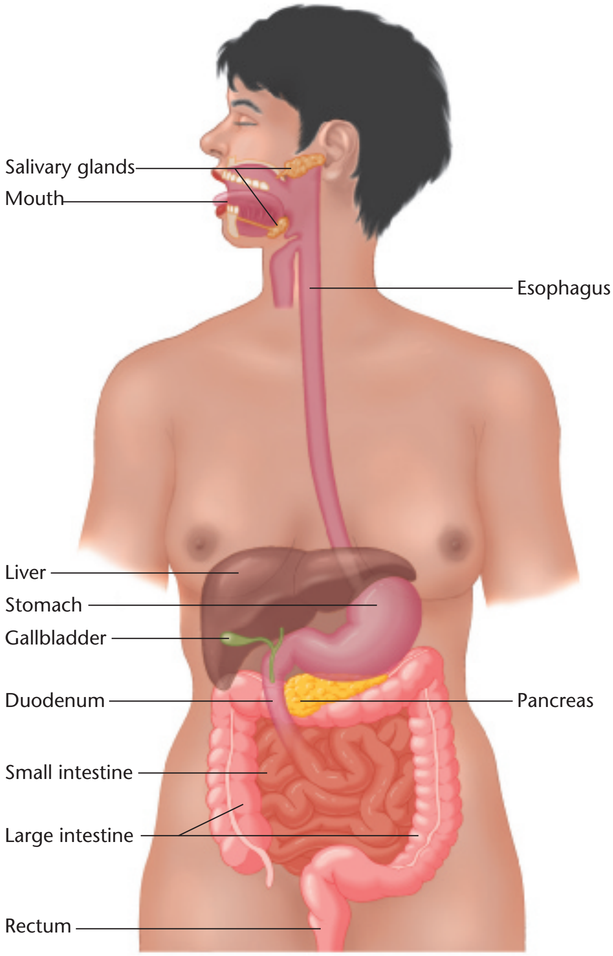
The digestive system, as diagramed in Figure 9.13, breaks food into molecules that the cells can use. In the mouth, enzymes in the saliva break down carbohydrates. Swallowed food travels down the esophagus to the stomach, where it mixes with hydrochloric acid and enzymes that digest proteins. The stomach stores food for a time, and then a round sphincter muscle opens to release food to the small intestine.

The small intestine has enzymes that digest proteins, fats, and carbohydrates. It absorbs digested materials into the blood, which carries them to cells that either use them or store them. The large intestine absorbs water and minerals and lubricates the remaining materials for excretion.

Consumption of Dairy Products

Newborn mammals survive at first on mother's milk. At about the age of weaning, most mammals lose the intestinal enzyme **lactase**, which is necessary for metabolizing **lactose**, the sugar in milk. Adult mammals can drink a little milk, but consuming too much causes stomach cramps, gas, and diarrhea (Ingram, Mulcare et al., 2009; Rozin and Pelchat, 1988). The declining level of lactase may be an evolved mechanism to encourage weaning at the appropriate time.

Figure 9.13 The human digestive system



Humans are a partial exception to this rule. Many adults have enough lactase levels to consume milk and other dairy products throughout life. However, the prevalence of the necessary genes varies. Nearly all the adults in China and surrounding countries are unable to metabolize lactose, as do varying numbers of people in other parts of the world (Curry, 2013; Flatz, 1987; Rozin and Pelchat, 1988). People who are lactose intolerant can consume a little milk, and larger amounts of cheese and yogurt, which are easier to digest, but they generally learn to limit their intake.

The genetic ability to metabolize lactose in adulthood is common in societies with a long history of domesticated cattle. Within Africa, the distribution of ability to digest lactose varies sharply from place to place. Whereas Europeans who can digest lactose in adulthood all have variants of the same gene, people in various parts of Africa have genes that differ from one another and from Europeans, indicating that genes for adult lactose digestion evolved independently several times as groups began domesticating cattle (Tishkoff et al., 2007). Figure 9.14 shows the distribution of lactose tolerance across the eastern hemisphere. About 25 percent of Native American adults can digest lactose. For other residents of the Americas, the probability of digesting lactose depends on the origins of their ancestors.

Stop & Check

12. Why do the genes for digesting lactose differ among parts of Africa?

See page 319 for the answer.

Food Selection and Behavior

Does your food selection change your behavior? Many people have unsubstantiated beliefs, such as the belief that eating sugar makes children hyperactive. The best way to test this claim is to have children eat snacks with sugar on randomly selected days and artificially sweetened snacks on other days, without telling them or anyone else what they received on a given day. Studies of this type have found no significant effect of sugar on children's activity level, play behaviors, or school performance (Ells et al., 2008; Milich and Pelham, 1986). The belief that sugar causes hyperactivity is an illusion based on people's tendency to see what they expect to see.

Another common misconception is that eating turkey causes sleepiness, supposedly because eating turkey increases the supply of tryptophan, which enables the brain to make serotonin and melatonin. That idea probably

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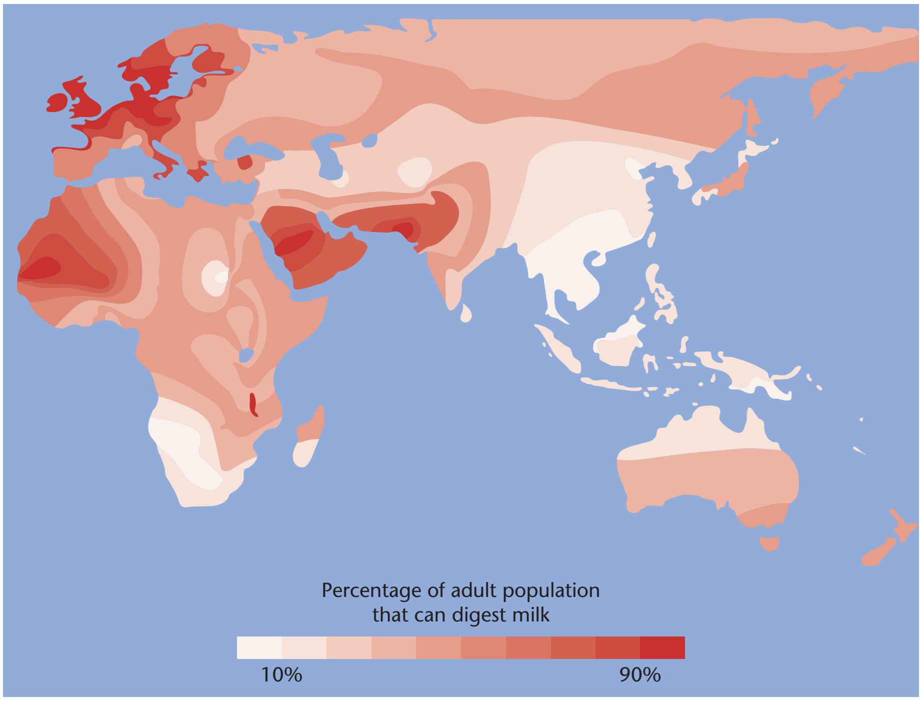
Figure 9.14 Percentage of adults who are lactose tolerant

People in areas with high lactose tolerance (e.g., Britain and Scandinavia) are likely to enjoy milk and other dairy products throughout their lives. Adults in areas with low tolerance (including Southeast Asia) drink less milk, if any.



(**Source:** Curry, 2013)

originated from the observation that many people in the United States feel sleepy after turkey dinner on Thanksgiving. However, turkey has only an average amount of tryptophan. The sleepiness on Thanksgiving afternoon results from overeating in general.

Nevertheless, it is true that tryptophan helps the brain produce melatonin, which aids sleepiness. Other than taking tryptophan pills, the most reliable way to increase tryptophan in the brain is to eat a diet high in carbohydrates. Here is the explanation: Tryptophan enters the brain by an active-transport protein that it shares with phenylalanine and other large amino acids. When you eat carbohydrates, your body reacts by increasing secretion of insulin, which moves sugars into storage, and also moves phenylalanine into storage, in liver cells and elsewhere. Reducing the competition from phenylalanine makes it easier for tryptophan to reach the brain, inducing sleepiness (Silber and Schmitt, 2010). In short, the dessert at your big meal induces sleepiness much more than turkey does.

On the other hand, the traditional belief that fish is brain food appears to be true. Many fish, especially salmon, contain oils that support brain functioning. Mothers who eat much seafood during pregnancy tend to have children who perform better on tests of cognitive ability (Julvez et al., 2016; Tahaei et al., 2022). Placebo-controlled studies confirm that the fatty acids in seafoods improve cognition in older people (Zhang et al., 2020).

Short- and Long-Term Regulation of Feeding

Getting enough food to eat is important, especially for your brain. When you are hungry, you find it hard to concentrate, and if you have been food deprived for a long time, it gets worse. Experimenters put mice on a severe diet that reduced their weight to 85 percent of normal. When energy levels get that low, the body reduces the fuel available to the brain. To continue generating action potentials without overburdening the sodium-potassium pump (which requires energy), the brain adjusts by bringing the resting potential of axons closer to their threshold for firing. That strategy comes at a cost: Because the resting potential is close to the threshold, the axon produces accidental action potentials, and the brain's processes become less precise. Vision becomes less sharp, for example (Padamsay et al., 2022), and presumably cognitive processes suffer equally, although the experimenters did not test it. In short, starving people suffer intellectually. Here, we are talking about severe and prolonged hunger, but if you feel like getting a snack right now, oh well, go ahead.

Figure 9.15 5,000-year-old gum

An archeology student in western Finland discovered this lump of birch bark tar that was used in chewing gum by a person living in the Neolithic era.

CB2/ZOB/WENN/Newscom

(**Source:** Reprinted by permission from Macmillan Publishers Ltd., "Plus c'est le meme chews," by Stephen Battersby, *Nature*, 1997.)

Oral Factors

You're a busy person, right? If you could get all the nutrition you need by swallowing a pill, would you do it? Once in a while perhaps, but not often. People like to eat. They also like to taste and chew. Figure 9.15 shows a piece of 5,000-year-old birch-bark tar that was used for making chewing gum. Anthropologists don't know how the ancient people removed the sap to make the gum, and they aren't sure why anyone would chew something that tasted as bad as this gum probably did (Battersby, 1997). Clearly, the urge to chew is strong.

Could you become satiated without tasting your food? In one experiment, college students consumed lunch five days a week by swallowing one end of a rubber tube and then using a button to pump a liquid diet into the stomach (Jordan, 1969; Spiegel, 1973). (Yes, they were paid for participating.) After a few days of practice, each person established a consistent pattern of pumping a constant volume of the liquid each day and maintaining a constant body weight. Most found the untasted meals unsatisfying and reported a desire to taste or chew something (Jordan, 1969).

Could you satisfy your hunger by taste alone? In **sham-feeding** experiments, everything an animal swallows leaks out of a tube connected to the esophagus or stomach. Sham-feeding animals eat and swallow almost continually without becoming satiated (G. P. Smith, 1998). In short, taste contributes to satiety, but it is not sufficient.

Stop & Check

13. What evidence showed that taste is not sufficient for satiety?

See page 319 for the answer.

The Stomach and Intestines

The main signal to end a meal is distension of the stomach. The importance of stomach distension explains why sham feeding does not satisfy hunger, and why eating satisfies your hunger before the nutrition reaches the cells that need it. Stomach distension was always a likely hypothesis to explain satiety, but it wasn't easy to demonstrate. In a decisive experiment, researchers attached an inflatable cuff at the connection between the stomach and the small intestine (Deutsch et al., 1978). Inflating the cuff prevented food from passing to the duodenum, and deflating it allowed it to pass again. Researchers carefully ensured that the cuff was not painful to the animal and did not interfere with feeding. When the cuff was inflated, an animal ate a certain amount and then stopped until the cuff was deflated. Evidently, stomach distension is sufficient to stop a meal. The **vagus nerve** (cranial nerve X) conveys information to the hypothalamus about the stretching of the stomach walls (Kim et al., 2020). However, people who have had their stomach surgically removed because of stomach cancer or other disease still report satiety, so stomach distension is not the only mechanisms of satiety.

The **duodenum** (DYOU-oh-DEE-num or dyuh-ODD-ehn-uhm), the part of the small intestine adjoining the stomach, is a major site for absorbing nutrients. Nerves from the duodenum inform the brain not only about distension, but also about the type and amount of nutrition. How do your intestines "know" what you ate? Your digestive tract has receptors similar to those on your tongue. They do not provide you with a conscious experience, but they alter brain activity to influence your satiety (Cvijanovic et al., 2015; van Avesaat et al., 2015). Animals that lack sweetness receptors on the tongue nevertheless develop a preference for sugary foods and liquids, because of their effect on receptors in the intestines (Tan et al., 2020).

Distension of the duodenum releases the hormone **cholecystokinin** (ko-leh-SIS-teh-KI-nehn) **(CCK)**, which produces satiety in two ways (Gibbs, Young, and Smith, 1973). First, CCK constricts the sphincter muscle between the stomach and the duodenum, causing the stomach to hold its contents and fill more quickly than usual (McHugh and Moran, 1985; Smith and Gibbs, 1998). In that way CCK hastens stomach distension. Second, CCK stimulates the vagus nerve to send signals to the hypothalamus, causing cells there to release a neurotransmitter that is a shorter version of the CCK molecule itself (Kobelt et al., 2006; Schwartz, 2000). The process is something like sending a fax: The CCK in the intestines cannot cross the blood–brain barrier, but it stimulates cells to release something almost like it.

Given that CCK helps to end a meal, could we use it to help people who are trying to lose weight? Unfortunately, no. CCK produces short-term effects only. It limits the size of the meal, but an animal that has eaten a smaller than usual meal compensates by overeating at the next meal, or by eating the next meal sooner (Cummings and Overduin, 2007).

Stop & Check

14. What evidence shows that stomach distension is sufficient for satiety?
15. What are two mechanisms by which CCK increases satiety?

See page 319 for the answer.

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Glucose, Insulin, and Glucagon

Digestion converts much of a meal into glucose, an important source of energy throughout the body and the brain's main fuel. Two pancreatic hormones, insulin and glucagon, regulate the flow of glucose into cells. Immediately before a meal (as you react to the sight and smell of the food), as well as during and after a meal, the pancreas releases **insulin**, which enables glucose to enter the cells. The brain cells are an exception to this rule, because glucose can enter them without need for insulin. Some of the glucose enters the liver, which converts it to glycogen and stores it. Some also enters fat cells, which convert it to fat and store it. The net effect of insulin prevents blood glucose levels from rising too sharply.

As time passes after a meal, the blood glucose level falls, insulin levels drop, glucose enters the cells more slowly, and hunger increases (Figure 9.16). The pancreas increases release of **glucagon**, stimulating the liver to convert some of its stored glycogen back to glucose.

Figure 9.16 Insulin and glucagon feedback system

When glucose levels rise, the pancreas releases the hormone insulin, which helps glucose enter cells, including liver cells and fat cells that store fuel for future use. The entry of glucose into cells suppresses hunger and decreases eating, thereby lowering the glucose level.

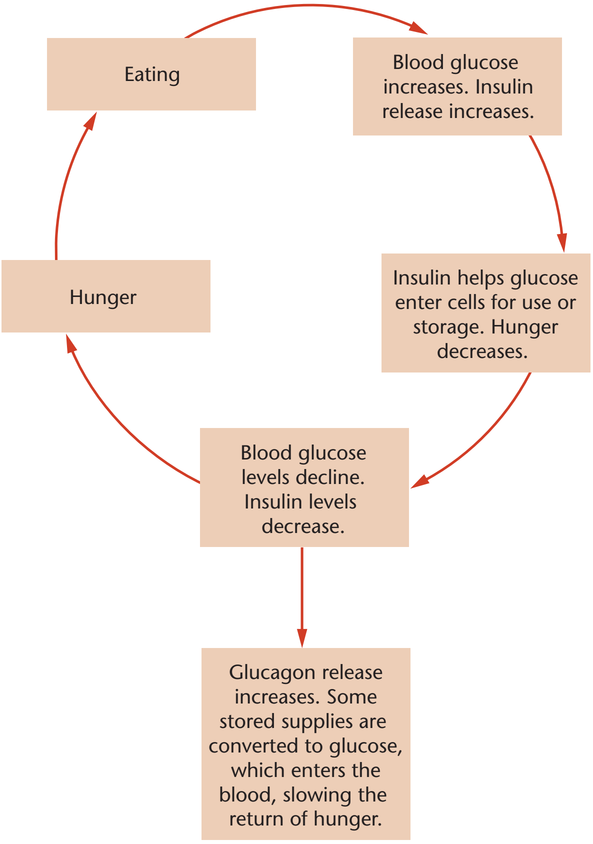
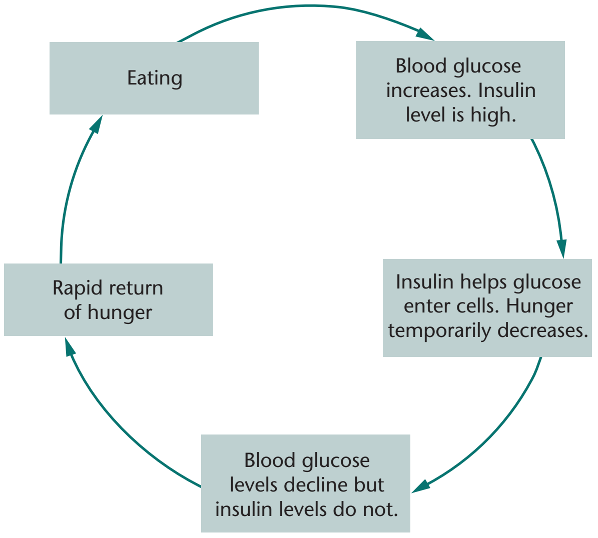

Eating
Blood glucose increases. Insulin release increases.
Insulin helps glucose enter cells for use or storage. Hunger decreases.
Blood glucose levels decline. Insulin levels decrease.
Glucagon release increases. Some stored supplies are converted to glucose, which enters the blood, slowing the return of hunger.
Hunger

Figure 9.17 Effects of steady high insulin levels on feeding

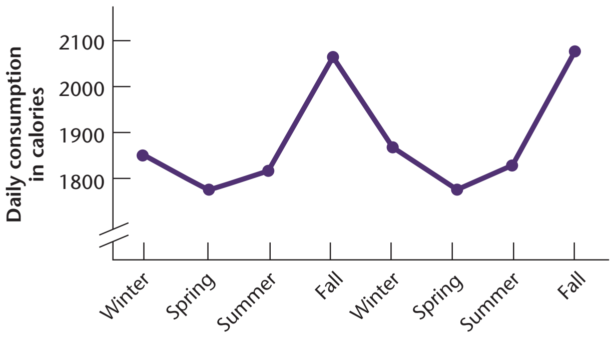
Constantly high insulin causes blood glucose to be stored as fats and glycogen. Because it becomes difficult to mobilize the stored nutrients, hunger returns soon after each meal.


Eating
Blood glucose increases. Insulin level is high.
Insulin helps glucose enter cells. Hunger temporarily decreases.
Blood glucose levels decline but insulin levels do not.
Rapid return of hunger

In autumn, animals that are preparing for hibernation have constantly high insulin levels. They rapidly deposit much of each meal as fat and glycogen, quickly grow hungry again, and continue gaining weight (Figure 9.17). That weight gain is a valuable preparation for a season when the animal will have to survive off its fat reserves. Most humans also eat more in autumn than in other seasons, as shown in Figure 9.18 (de Castro, 2000). In the United States, we tend to blame our autumn weight gain on the Halloween and Thanksgiving holidays, but the real reason may be an evolved drive to

Figure 9.18 People eat more in fall than in other seasons

Mean intake increases by more than 10 percent, according to people's eating diaries.



(**Source:** Modified from de Castro, J. M., 2000, Eating behavior: Lessons from the real world of humans. *Nutrition*, *16*, 800–813.)

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increase our reserves in preparation for winter. In earlier times, food was scarce in winter.

Diabetes and Appetite

Diabetes is a disorder of glucose absorption. In **Type 1 diabetes**, sometimes called *juvenile diabetes* because it usually begins early in life, an autoimmune attack reduces or eliminates the ability of the pancreas to produce insulin. Type 1 diabetes requires treatment by injections or a pump to provide the needed insulin. It also requires the person to maintain a careful diet, minimizing intake of sugars. Because the restricted diet is difficult, eating disorders are common, especially for adolescents (Signal and Hofman, 2022). **Type 2 diabetes**, which usually begins in middle age or later, is the more common type. It occurs mostly in association with obesity and lack of exercise. In Type 2 diabetes, the pancreas produces enough insulin, but cells have become unresponsive to it. Treatment includes restricted diet, increased exercise, and medications.

With either type of diabetes, if untreated, the blood glucose level rises, sometimes to harmful levels, but not much glucose enters the cells (Figure 9.19). Because the cells are starving, hunger increases and eating increases, but the person continues losing weight.

Stop & Check

16. Why do people with very low insulin levels eat so much? Why do people with constantly high levels eat so much?

See page 319 for the answer.

Figure 9.19 People with untreated diabetes eat much but lose weight

Because the glucose in the blood cannot enter the cells, people excrete glucose in their urine while the cells are starving.

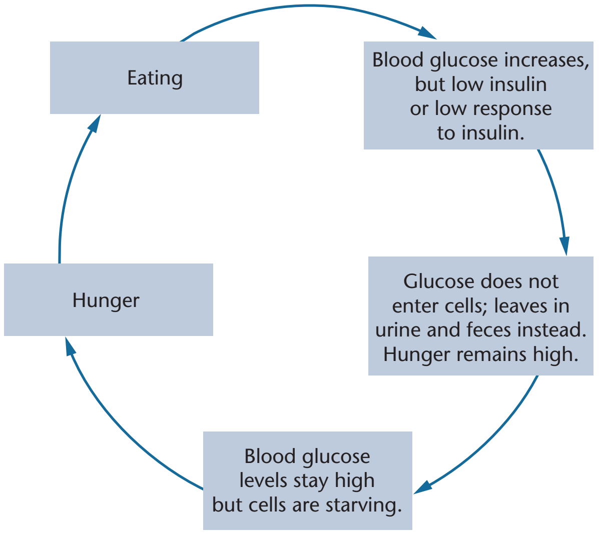
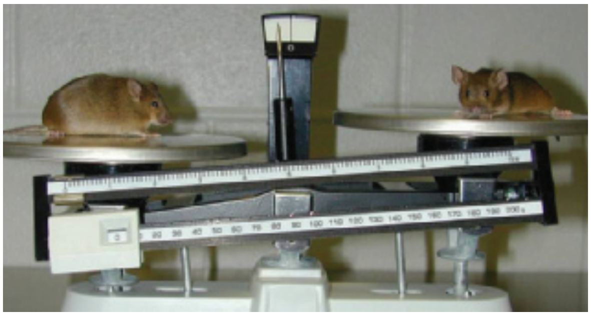

Eating
Blood glucose increases, but low insulin or low response to insulin.
Glucose does not enter cells; leaves in urine and feces instead. Hunger remains high.
Blood glucose levels stay high but cells are starving.
Hunger

Figure 9.20 The mouse on the left has a mutation in the *leptin* gene

Mice with this gene eat more, move less, and gain weight.



Lexicon Genetics Incorporated/Wikimedia Commons

(**Source:** Reprinted with permission from Macmillan Publishers Ltd. from, "Positional cloning of the mouse obese gene and its human homologue, by Zhang et al., 1994, *Nature*, 372, 425–432.)

Leptin

Taste, stomach distension, duodenum distension, and insulin help regulate the onset and offset of a meal. However, we cannot expect those mechanisms to be completely accurate. Imagine what would happen if you consistently ate just a bit too little or just a bit too much. The body needs a long-term mechanism to compensate for day-to-day mistakes.

It does so by monitoring fat supplies. Researchers had long suspected some kind of fat monitoring, but they discovered the actual mechanism by accident. They found that mice of a particular genetic strain consistently become obese, as shown in Figure 9.20 (Zhang et al., 1994). After researchers identified the responsible gene, they found the peptide it makes, a previously unknown hormone that they named **leptin**, from the Greek word *leptos,* meaning "slender" (Halaas et al., 1995). Unlike insulin, which is so evolutionarily ancient that we find it throughout the animal kingdom, leptin is limited to vertebrates (Morton et al., 2006). In genetically normal vertebrates, the body's fat cells produce leptin. An increase in fat cells means more leptin. Mice with a mutation in the *leptin* gene fail to produce leptin.

Leptin signals your brain about your fat reserves. When your fat reserves decrease, leptin levels decline, and you react by eating more and becoming less active, to save energy. When leptin levels return to normal, you eat less and become more active (Campfield et al., 1995; Elias et al., 1998). In adolescence, a certain level of leptin triggers the onset of puberty. On average, thinner people enter puberty later. If your fat supply is too low to provide for your own needs, you don't have enough energy to provide for a baby.

Because a mouse with a mutation in the *leptin* gene does not make leptin, its brain reacts as if its body has no fat stores and must be starving. The mouse eats as much as possible, conserves its energy by not moving much, and

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fails to enter puberty. Injections of leptin reverse all these symptoms (Pelleymounter et al., 1995).

As you might imagine, news of this research inspired pharmaceutical companies to hope they could make a fortune by selling leptin. After all, the body makes leptin all the time, so it should have no unpleasant side effects. Leptin does help those rare people who are genetically unable to make leptin. However, most overweight people already produce plenty of leptin, and giving them extra leptin produces little change in their appetite (Considine et al., 1996). At first, the interpretation was that overweight people must have developed a resistance to insulin. However, later research found that extra leptin also produces little effect on normal-weight people. Low levels of leptin trigger hunger, but beyond a certain level, additional leptin has only a slight effect (Ravussin et al., 2014). In general, the mechanisms that promote hunger are stronger and more insistent than those for satiety. Evolution has apparently prepared us to avoid starvation more vigorously than to avoid excess.

Stop & Check

17. Why are leptin injections less helpful for most overweight people than for mice with a mutation in the *leptin* gene?

See page 319 for the answer.

Brain Mechanisms

Hunger depends on the contents of your stomach and intestines, the availability of glucose to the cells, your body's fat supplies, your health and body temperature, and the availability of appealing food. Just seeing a picture of tasty food increases your appetite (Harmon-Jones and Gable, 2009). People eat more on weekends than on other days, and more when eating with friends or family than when eating alone (de Castro, 2000). All these types of information converge onto several nuclei of the hypothalamus (Figure 9.6).

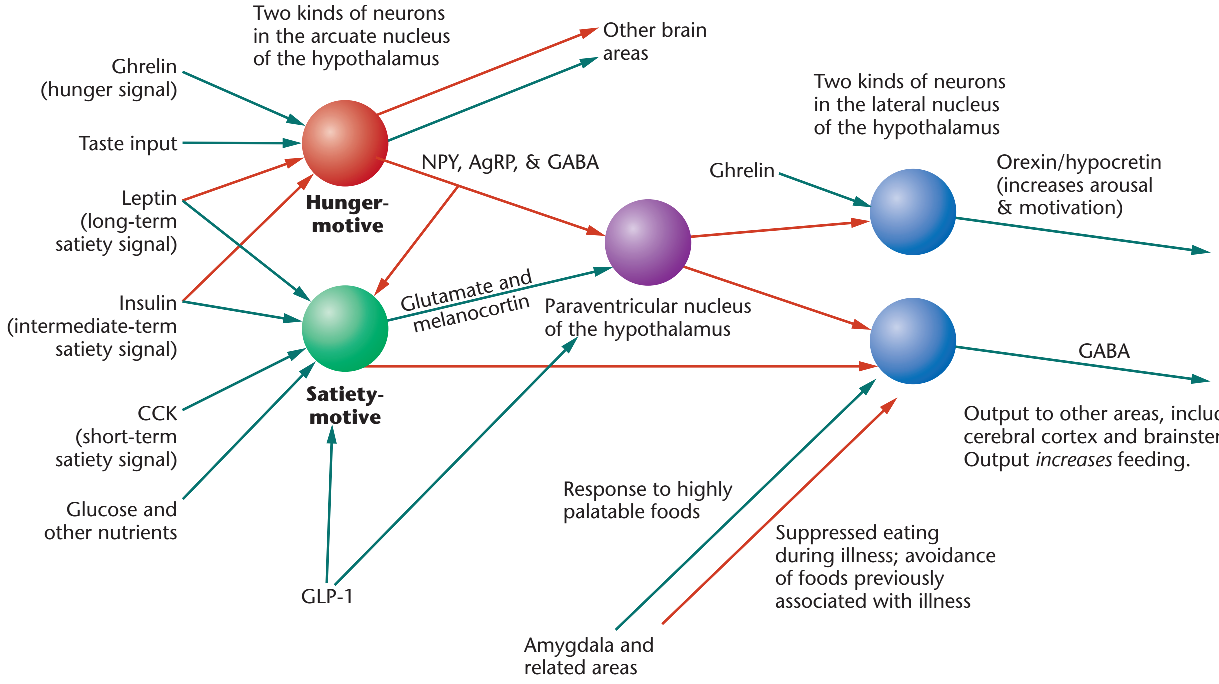
Figure 9.21 shows how information impinges onto two kinds of cells in the arcuate nucleus of the hypothalamus, regarded as the master area for controlling appetite (Mendieta-Zéron et al., 2008). The arcuate nucleus then controls other areas of the hypothalamus. Admittedly, this figure may look intimidating. Let's go through it step by step.

The Arcuate Nucleus and Paraventricular Hypothalamus

The **arcuate nucleus** of the hypothalamus has one set of neurons sensitive to hunger signals and another set sensitive to satiety signals. Most journal articles refer to the first set as the "NPY/AgRP" neurons and the second set as the "POMC/CART" neurons (because of neuromodulators that they

Figure 9.21 The feeding circuit in the hypothalamus

Excitatory connections are in green and inhibitory connections are in red. Hunger signals increase feeding by inhibiting the inhibitory messages from the paraventricular nucleus to the lateral hypothalamus. GLP-1 is glucagon-like protein 1, a neuromodulator.


Two kinds of neurons
in the arcuate nucleus
of the hypothalamus
Other brain
areas
Ghrelin
(hunger signal)
Taste input
Leptin
(long-term
satiety signal)
Insulin
(intermediate-term
satiety signal)
CCK
(short-term
satiety signal)
Glucose and
other nutrients
Hunger-
motive
Satiety-
motive
NPY, AgRP, & GABA
Glutamate and
melanocortin
Paraventricular nucleus
of the hypothalamus
GLP-1
Two kinds of neurons
in the lateral nucleus
of the hypothalamus
Ghrelin
Orexin/hypocretin
(increases arousal
& motivation)
GABA
Output to other areas, including
cerebral cortex and brainstem.
Output *increases* feeding.
Response to highly
palatable foods
Suppressed eating
during illness; avoidance
of foods previously
associated with illness
Amygdala and
related areas

(**Source:** Based on Biddinger et al., 2020; Farkas et al., 2021; Horvath, 2005; Minokoshi et al., 2004; O'Connor et al., 2015.)

release), but for simplicity this text refers to them as hunger neurons and satiety neurons. Input to these cells comes from hormones such as insulin and leptin, and also from cells in the amygdala and other brain areas (Cai et al., 2014; Herman et al., 2016; Labouèbe et al., 2016; Vachez et al., 2021).

Part of the input to the hunger-sensitive cells comes from axons releasing the neurotransmitter **ghrelin** (GRELL-in). This odd-looking word takes its name from the fact that it binds to the same receptors as growth-hormone releasing hormone (GHRH). During food deprivation, ghrelin triggers stomach contractions. Ghrelin also acts on the hypothalamus to increase appetite. People who produce greater than average amounts of ghrelin respond more strongly than average to the sight of food, and they are almost twice as likely as other people to become obese (Karra et al., 2013). Another input to the hunger-sensitive cells represents taste and related cues. Even the sight and smell of food stimulates these cells, produces reward, and facilitates learning to find food (Berrios et al., 2021).

The satiety-sensitive cells receive input from leptin, CCK, blood glucose, and insulin (Fan et al., 2004; Parton et al., 2007). Nicotine also stimulates the satiety neurons (Mineur et al., 2011). The result is that cigarette smoking decreases appetite, and quitting smoking increases appetite.

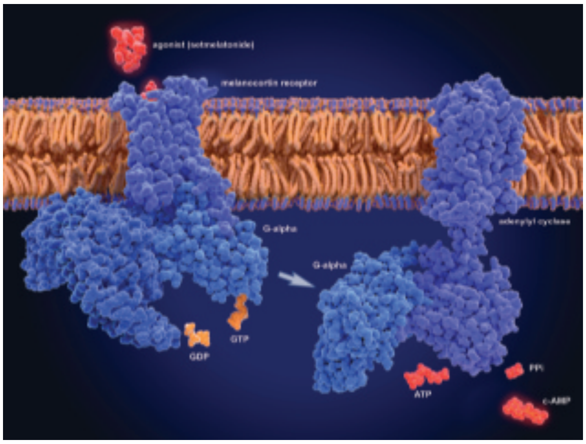
From the arcuate nucleus in Figure 9.21, notice the double negative: Hunger cells nucleus inhibit the paraventricular nucleus, and the paraventricular nucleus inhibits the lateral hypothalamus (Sutton et al., 2014). The inhibition of inhibition means greater excitation in the lateral hypothalamus, a key area for eating. After strong enough inhibition of the paraventricular nucleus, rats eat huge meals (Billington and Levine, 1992; Leibowitz and Alexander, 1991; Morley et al., 1985). Output from the hunger cells also inhibits areas that facilitate sexual behaviors and responses to itch and inflammatory pain (Alhadeff et al., 2018, 2020; Padilla et al., 2016). If you are starving, you spend your time searching for food instead of sex, and you don't waste your energy by scratching that itchy spot. First things first.

Axons from the satiety-sensitive cells of the arcuate nucleus excite the paraventricular nucleus, releasing **melanocortins** (Ellacott and Cone, 2004) and glutamate (Fenselau et al., 2017). Melanocortin receptors in the paraventricular nucleus are important for limiting food intake, and anything that damages these receptors leads to overeating (Asai et al., 2013; Huszar et al., 1997; Figure 9.22). Researchers have not yet found a drug that stimulates melanocortin receptors enough to inhibit appetite without unacceptable side effects. The amygdala and related areas send two kinds of input that modify activity in the lateral hypothalamus based on emotional responses to the food (Carter et al., 2013; Douglass et al., 2017); Jennings et al., 2013; Mohammad et al., 2021).

An additional pathway from the lateral hypothalamus releases orexin (Fu, Acuna-Goycolea, and van den Pol, 2004). In addition to its role in wakefulness, orexin increases activity in general, including persistence in seeking food (Mahler et al., 2014; Williams et al., 2004).

Figure 9.22 Activation of a melanocortin receptor at a metabotropic synapse

When melanocortin or a drug mimicking it attaches to the receptor, as on the left, it releases a G protein inside the neuron, as on the right. Activating this receptor decreases appetite. People with an impaired form of the receptor are prone to overeating.



Juan Gaertner/Science Source

As you can see, many chemicals and brain areas contribute to feeding and satiety. If the control of feeding fails in one way, the brain has other mechanisms to compensate for it.

Stop & Check

18. Name three hormones that increase satiety and one that increases hunger.
19. How does the inhibitory transmission from the hunger cells lead to increased eating?
20. What is the role of melanocortins?

See page 319 for the answer.

The Lateral Hypothalamus

Output from the paraventricular nucleus acts on the **lateral hypothalamus** (Figure 9.23), which includes so many neuron clusters and passing axons that it has been compared to a crowded train station (Leibowitz and Hoebel, 1998). The lateral hypothalamus controls insulin secretion, alters taste responsiveness, and facilitates feeding in other ways. An animal with damage in this area refuses food and water, averting its head as if the food were distasteful. It may starve to death unless it is force-fed, but if kept alive, it gradually recovers much of its ability to eat (Figure 9.24). In contrast, stimulation of the lateral hypothalamus increases the drive to eat.

Damage to the lateral hypothalamus not only kills the neurons there, but also interrupts axons containing

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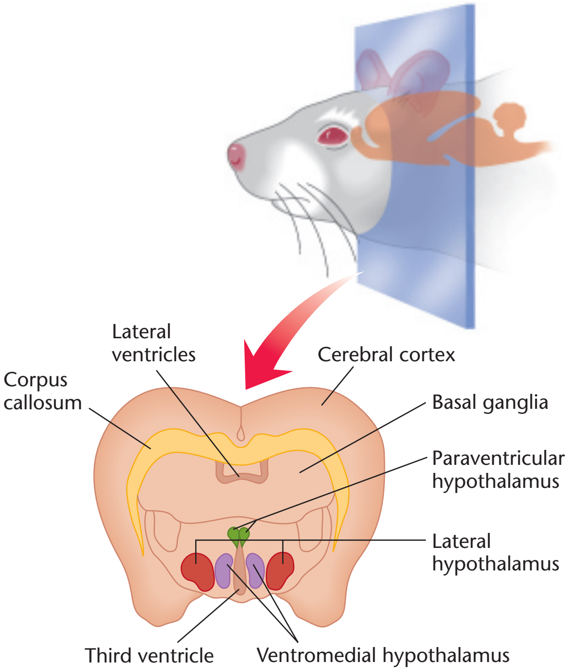
Figure 9.23 The lateral hypothalamus, ventromedial hypothalamus, and paraventricular hypothalamus

The side view above indicates the plane of the coronal section of the brain below it.



(**Source:** Based on Hart, 1976)

dopamine that pass through the area. To separate the roles of hypothalamic cells from those of passing fibers, experimenters used chemicals that damage only the cell bodies, or induced lesions in very young rats, before the dopamine axons reached the lateral hypothalamus. In both cases, damaging the cell bodies produced a loss of feeding without impairing arousal or activity (Almli et al., 1979; Grossman et al., 1978; Stricker et al., 1978). In contrast, the axons passing through the lateral hypothalamus contribute to arousal, activity, and reward (Stuber and Wise, 2016). Figure 9.25 shows the ways in which the lateral hypothalamus promotes eating:

- Axons to the NTS (nucleus of the tractus solitarius), part of the taste pathway, enhance the responses to pleasant tastes and increase salivation.
- Axons into several parts of the cerebral cortex facilitate ingestion and swallowing and increase responses to the taste, smell, or sight of food (Critchley and Rolls, 1996).
- Axons to the spinal cord control digestive secretions (van den Pol, 1999).

Stop & Check

21. How does the lateral hypothalamus facilitate feeding?

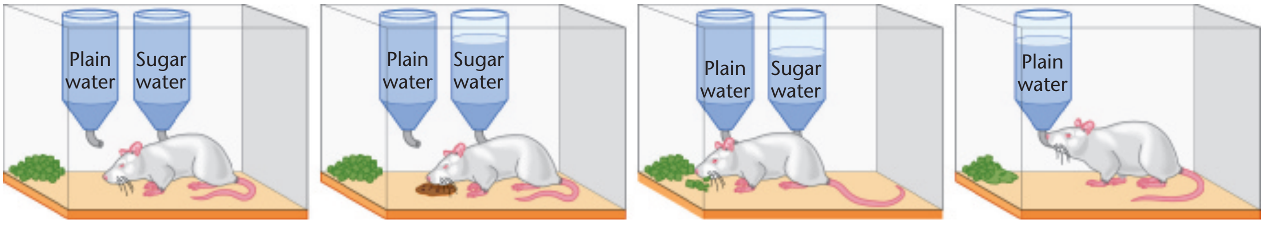
See page 319 for the answer.

Medial Areas of the Hypothalamus

Output from the **ventromedial hypothalamus (VMH)** inhibits feeding (Chee, Myers, Price, and Colmers, 2010), and therefore damage around this nucleus leads to overeating and weight gain (Figure 9.23). Some people with a tumor in the area have gained more than 10 kg (22 lb) per month (Al-Rashid, 1971; Killeffer and Stern, 1970; Reeves and Plum, 1969). Rats with similar damage sometimes double or triple their weight (Figure 9.26). Although these symptoms have been known as the *ventromedial hypothalamic*

Figure 9.24 Recovery after damage to the lateral hypothalamus

At first, the rat refuses all food and drink. If kept alive by force-feeding, it gradually recovers its ability to eat and drink enough to stay alive. However, even at the final stage of recovery, its behavior is not fully normal.



Stage 1. Aphagia and adipsia. Rat refuses all food and drink; must be force-fed to keep it alive.

Stage 2. Anorexia. Rat eats a small amount of palatable foods and drinks sweetened water. It still does not eat enough to stay alive.

Stage 3. Adipsia. The rat eats enough to stay alive, though at a lower-than-normal body weight. It still refuses plain water.

Stage 4. Near-recovery. The rat eats enough to stay alive, though at a lower-than-normal body weight. It drinks plain water, but only at mealtimes to wash down its food. Under slightly stressful conditions, such as in a cold room, the rat will return to an earlier stage of refusing food and water.

(**Source:** Based on Teitelbaum and Epstein, 1962)

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Figure 9.25 Pathways from the lateral hypothalamus

Axons from the lateral hypothalamus modify activity in several other brain areas, changing the response to taste, facilitating ingestion and swallowing, and increasing food-seeking behaviors. Also (not shown), the lateral hypothalamus controls stomach secretions.

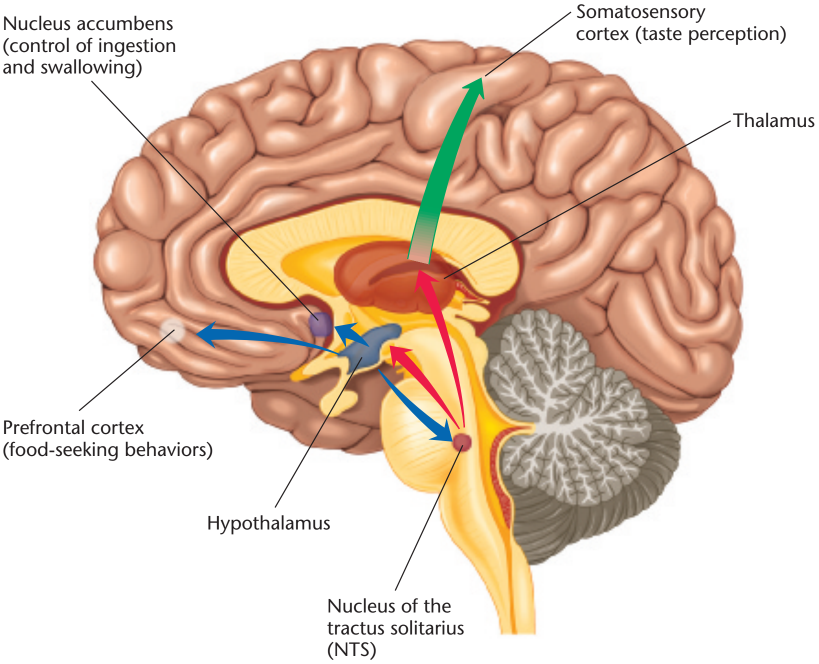
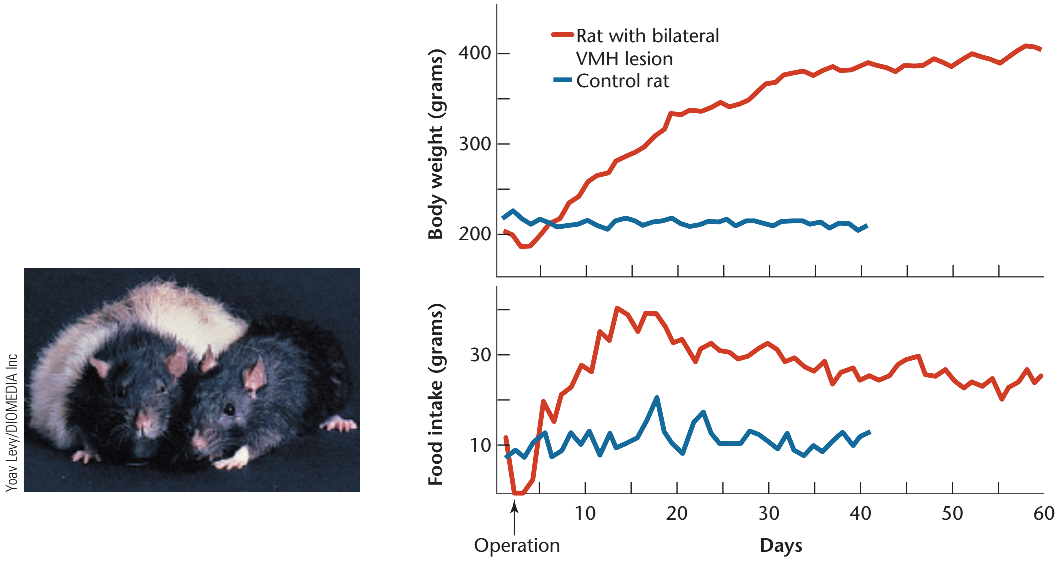

Nucleus accumbens
(control of ingestion
and swallowing)
Somatosensory
cortex (taste perception)
Thalamus
Prefrontal cortex
(food-seeking behaviors)
Hypothalamus
Nucleus of the
tractus solitarius
(NTS)

Figure 9.26 Effects of damage to the ventromedial hypothalamus

(a) On the left is a rat with damage to the ventromedial hypothalamus. **(b)** Weight and eating after damage to the ventromedial hypothalamus. Within a few days after the operation, the rat begins eating much more than normal.



(a)

(b)

(**Source:** Reprinted by permission of the University of Nebraska Press from “Disturbances in feeding and drinking behavior after hypothalamic lesions,” by P. Teitelbaum, pp. 39–69, in M. R. Jones, Ed., 1961, *Nebraska Symposium on Motivation*. Copyright © 1961 by the University of Nebraska Press. Copyright © renewed 1988 by the University of Nebraska Press.)

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Table 9.2 | Effects of Hypothalamic Lesions

Hypothalamic Area	Effect of Lesion
Preoptic area	Deficit in physiological mechanisms of temperature regulation
Lateral preoptic area	Deficit in osmotic thirst due partly to damage to cells and partly to interruption of passing axons
Lateral hypothalamus	Undereating, weight loss, low insulin level (because of damage to cell bodies); underarousal, underresponsiveness (because of damage to passing axons)
Ventromedial hypothalamus	Increased meal frequency, weight gain, high insulin level
Paraventricular nucleus	Increased meal size, especially increased carbohydrate intake during the first meal of the active period of the day

syndrome, damage limited to just the ventromedial hypothalamus does not consistently increase eating or body weight. To produce obesity, the lesion must extend outside the ventromedial nucleus to invade nearby axons (Ahlskog and Hoebel, 1973; Ahlskog et al., 1975; Gold, 1973).

Recall that rats with damage to the paraventricular nucleus eat larger than average meals. In contrast, those with damage in and around the ventromedial area eat normal-sized meals, but they eat more frequently (Hoebel and Hernandez, 1993). One reason is that they have increased stomach motility and secretions, and their stomach empties faster than normal. The faster the stomach empties, the sooner the animal is ready for its next meal. Another reason is that the damage increases the production of insulin, which keeps moving glucose into storage, even when the blood glucose level is low (King et al., 1984). Even though the animal is gaining weight, most of the body's cells are starving for nutrition. The result is increased hunger. According to Mark Friedman and Edward Stricker (1976), the problem is not that the rat gets fat from overeating. Rather, the rat overeats because it is storing so much fat.

Table 9.2 summarizes the effects of lesions in several areas of the hypothalamus.

Stop & Check

22. In what way does eating increase after damage in and around the ventromedial hypothalamus? After damage to the paraventricular nucleus?

See page 319 for the answer.

Eating Disorders

Obesity has become increasingly prevalent in much of the world. At one time psychologists assumed that obesity was a reaction to psychological distress. A review of 15 longitudinal studies found that depression increased the probability of obesity, and that obesity increased the probability of depression (Luppino et al., 2010), but both effects were small. One study found obesity in 19 percent of people with a history of depression and in 15 percent of those who had never suffered depression (McIntyre et al., 2006). Another study found that the average adult with depression gained about a pound per year, whereas the average for everyone else was about 8/10 of a pound (Brumpton et al., 2013). So, emotions are merely one contributor, and usually not a large one.

Another influence is prenatal environment. Many studies have found that the children of obese mothers are more likely than average to become obese themselves. That observation is consistent with both genetic and environmental explanations. Researchers using laboratory animals randomly assigned pregnant females to a control diet or a diet that produces obesity. The offspring from obese females developed changes in their hypothalamic anatomy and their insulin responses that increased their own probability of obesity (Kislal et al., 2020).

Genetic Influences

Studies of twins and adopted children in many countries have consistently found high heritability of body weight (Albuquerque et al., 2015; Min et al., 2013; Silventoinen et al., 2016). Researchers distinguish three types of heritability for obesity. *Syndromal* obesity results when genes cause a medical problem that includes obesity. For example, Prader-Willi syndrome is marked by mild cognitive disabilities, short stature, and obesity, with of course variation among individuals. People with this syndrome have blood levels of ghrelin four to five times higher than average (Cummings et al., 2002). Ghrelin, you will recall, is a peptide related to hunger. The fact that people with Prader-Willi syndrome overeat and still produce high ghrelin levels suggests that their problem relates to an inability to turn off ghrelin release.

A second type, *monogenic* obesity, occurs when a single gene causes obesity without other physical or mental abnormalities. The most common type of monogenetic obesity comes from a mutation in the gene for the melanocortin receptor (important for satiety) (Mergen et al., 2001). Several other rare genes can also cause monogenic obesity (van der Klaauw and Farooqi, 2015). Still, single-gene mutations account for only a few percent of cases of obesity (Yeo and Heisler, 2012).

The third type, *polygenic* or *common* obesity, relates to many genes that slightly or moderately increase the probability of obesity. The most influential common gene is known as the FTO gene, which exists in many variants (Sobreira et al., 2021). Unlike monogenetic obesity, variations in the FTO gene do not always lead to obesity, but they increase the probability (Abd Ali et al., 2021; Frayling et al., 2007). Researchers have identified many other genetic variants that increase or decrease the probability of obesity (Akbari et al., 2021).

The effects of a gene depend on the environment. Consider the Native American Pima of Arizona and Mexico. Most are seriously overweight, and researchers identified several genes associated with the increased risk (Bian et al., 2010; Muller et al., 2010). However, obesity was uncommon among them in the early 1900s, when their diet consisted mostly of desert plants that ripen in the brief rainy season. The Pima apparently evolved a strategy of eating all they could when food was available, because it would have to carry them through periods of scarcity. They also evolved a tendency to conserve energy by limiting their activity. Now, eating a more typical U.S. diet that is high in calories, the strategy of overeating and inactivity is maladaptive. In short, weight gain depends on both genes and environment.

Stop & Check

23. Why did the Pima begin gaining weight in the mid-1900s?

See page 319 for the answer.

Weight Loss Techniques

You will hear advocates of a diet plan brag that many people on their plan lost a significant amount of weight. That statement may be true, but it means little unless we know how long they kept the weight off, or how many other people tried the plan and failed to lose weight. Many psychologists recommend small changes in diet ("eat a little less than usual") on the expectation that more people will stick to this diet (Stroebele et al., 2008). Exercise is important, and it need not be strenuous, but it needs to be consistent, such as a long brisk walk on most days (Wyatt, 2013).

Several well-meaning attempts to combat obesity have failed to help. Around 1970, American companies began sweetening beverages with high-fructose corn syrup instead of sucrose. Fructose is sweeter than sucrose, and the hope was that people could satisfy their craving for sweets with fewer calories. Since then, obesity became more common, not less. Another idea was to sweeten beverages with nonnutritive sweeteners, in hopes of satisfying a craving for sweets without any calories at all. Again, obesity increased since the advent of zero-calorie soft drinks. Apparently, there is no such thing as satisfying a craving for sweet tastes.

Several companies market over-the-counter supplements to increase energy or decrease weight. A study found that fourteen such supplements contain oxilofrine, a stimulant never approved by the Food and Drug Administration. Many of the supplements fail to list it on the label. Athletes have been banned from participations when they tested positive for this drug, often without knowing that they had been taking it (Cohen et al., 2017).

Some people who get discouraged about dieting turn to weight-loss drugs. For many years, the available weight-loss drugs produced only small benefits, often with harmful side effects. In 2021, the FDA approved semaglutide (Wegovy™), which binds to brain receptors sensitive to glucagon-like peptide 1 (GLP-1). A placebo-controlled study found that combining semaglutide with a program of exercise and a low-calorie diet led to a mean loss of 16 percent of body weight, with side effects that most people found tolerable (Wadden et al., 2021). Recall that glucagon is a pancreatic hormone that increases the release of glucose into the blood. As Figure 9.21 shows, GLP-1 increases activity in the satiety areas of the hypothalamus (Biddinger et al., 2020; Farkas et al., 2021).

Still another option is gastric bypass surgery, in which part of the stomach is sewed off so that food cannot enter. Remember that stomach distension is a major contributor to satiety. By decreasing stomach size, the surgery makes it possible for a smaller meal to produce satiety. The surgery poses enough risk that it is recommended only in the most serious cases of obesity, but in about two-thirds of cases, it does help people lose weight, improve their blood pressure, and decrease the risk of type 2 diabetes (Puzziferri et al., 2014).

Here is still another option, experimental and controversial: People's digestive systems have microorganisms that help digest the foods and perform many other functions, some helpful to us and some harmful. The types of microorganisms found in people with obesity differ from those in leaner people. Small-sample experiments with both mice and humans have shown that transferring intestinal microorganisms from lean to overweight individuals produces at least temporary benefits (Mocanu et al, 2021; Ridaura et al., 2013).

Stop & Check

24. Why are over-the-counter weight-loss supplements risky?

See page 319 for the answer.

Bulimia Nervosa

Bulimia nervosa is a condition in which people alternate between strict dieting and binges of overeating. Many, but not all, induce themselves to vomit, engaging in bingeing and purging. In the United States, the prevalence of bulimia is about 1 percent of women and 0.1 percent of men (Hoek

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and van Hoeken, 2003). A major contributor to this problem is the cultural pressure on people, especially women, to be thin. Bulimia nervosa has been recorded only in cultures with a strong western influence, and cases are known where it began to occur after the introduction of American movies and television programs (Keel and Klump, 2003).

On average, people with bulimia show a variety of biochemical abnormalities, including increased production of ghrelin, a hormone associated with increased appetite (Monteleone et al., 2010). The biochemistry is almost certainly a result of the binges and purges, rather than a cause. After therapy that decreases the symptoms of bulimia, the body chemicals return toward normal levels (Tanaka et al., 2006).

In several ways, bulimia resembles drug addiction (Hoebel et al., 1999). Eating tasty foods activates the same brain areas as addictive drugs, such as the nucleus accumbens (Volkow et al., 2017). Drug addicts who cannot get drugs sometimes overeat instead, and food-deprived people or animals become more likely than others to use drugs.

Researchers examined rats that were food deprived for 12 hours a day, including the first 4 hours of their wakeful period, and then offered a very sweet, syrupy sugar solution. Over several weeks on this regimen, the rats drank more and more each day, especially during the first hour of availability each day. The intake released dopamine and opioid (opiatelike) compounds in the brain, just as highly addicting drugs do (Colantuoni et al., 2001, 2002). The intake also increased the levels of dopamine type 3 receptors in the brain—again, resembling the effect of taking morphine (Spangler et al., 2004). If the rats were then deprived of this sweet liquid, they showed withdrawal symptoms, including head shaking, teeth chattering, and tremors. An injection of morphine relieved these symptoms. In short, the rats showed indications of an addiction to big doses of sugar (Avena et al., 2008). Similarly, we can regard bulimic cycles of dieting and binge eating as an addiction.

Anorexia Nervosa

Anorexia nervosa is characterized by a refusal to eat enough to maintain a healthy body weight. It sometimes becomes life threatening. Because the condition varies in severity, estimates of prevalence also vary, depending on the diagnostic criteria (Martinez-Gonzalez et al., 2020). However, the research agrees that anorexia is much more common among females than males, and that the onset is usually in the teenage years.

People with anorexia do not regard food as tasting bad. Rather, they express an exaggerated fear of growing fat. When they eat, they strongly prefer low-fat, low-calorie foods (Foerde et al., 2015). Contrary to what we might expect of people verging on starvation, those with anorexia generally engage in vigorous physical activity.

The American Psychiatric Association (2013) lists anorexia nervosa as a mental disorder, but depending on the definition of mental disorder, not everyone agrees. Although most people with anorexia experience some degree of anxiety or depression, few people had a noticeable disorder before the anorexia (Bühren et al., 2014; Lloyd et al., 2019; Zerwas et al., 2013). Furthermore, the treatments that are effective for depression or anxiety produce little if any benefit for anorexic patients. It is more likely that anorexia leads to anxiety or depression than that any psychiatric problem leads to anorexia (Sodersten et al. 2019; Troscianko and Leon, 2020). Brain research has found abnormalities of dopamine release in anorexia, but the brain abnormalities are more likely a result of weight loss than a cause (Sodersten et al., 2016).

An alternative view is that the primary problem is the weight loss itself. It is surprisingly simple to model some of the primary symptoms of anorexia in rats: Just put a rat on a diet of eating just one hour per day, keep it in a cool room, and provide a running wheel. The room temperature is a critical part of the procedure. Within an hour or two after the meal, a rat starts to feel cold and reacts by running in the wheel, generating body heat but also burning calories. On this schedule, a rat loses a little weight each day. In a warmer room, the rat would spend little time in the running wheel and would maintain its weight, even on this diet of eating only one hour per day (Gutiérrez, 2013). After a rat has lost a fair amount of weight, it stops eating even when food is available, and it can die of starvation in the presence of good food. Here is another example of temperature regulation influencing behavior in a surprising way, as in the first module.

So, one hypothesis is that someone who diets to lose weight will start exercising heavily to keep warm (Carrera et al., 2012), with the result of losing more weight. A treatment based on this idea starts by keeping the person warm, either by wearing a jacket or staying in a warm room. Physical exercise is strictly limited. Then the focus is to change eating behaviors (Troscianko and Leon, 2020), to train the person to eat at a normal, average pace. Six European clinics tried this approach with 571 patients. Within 13 months, three-fourths were fully recovered, and none had died (Bergh et al., 2013). That success rate is far better than what any other treatment can claim. Certainly, more research is necessary. So far, this approach is not well known in North America. But now you know about it.

Stop & Check

25. What evidence from rats suggests that bulimia resembles an addiction?
26. If rats are limited to eating for one hour a day, what determines whether or not they will lose weight?

See page 319 for the answer.

Module 9.3 | In Closing

The Multiple Controls of Hunger

The brain mechanisms for eating attend to taste, blood glucose, stomach distension, duodenal contents, body weight, fat cells, hormones, body temperature, social influences, and more. Because the system is so complex, it can produce errors in many ways. However, the complexity of the system also provides a kind of security: If one part of the system makes a mistake, another part can counteract it. The regulation of eating succeeds not in spite of its complexity but because of it.

Summary

1. The ability to digest a food is one major determinant of preference for that food. For example, people who cannot digest lactose generally do not like to eat dairy products. **306**
2. Widespread beliefs that sugar causes hyperactivity and that turkey causes sleepiness are unfounded. However, research does support the idea that eating fish is good for brain functioning. **306**
3. People and animals eat partly for the sake of taste. However, a sham-feeding animal, which tastes its foods but does not absorb them, eats almost constantly. Taste is not sufficient to satisfy hunger. **308**
4. In addition to taste, other factors controlling hunger include distension of the stomach and intestines, secretion of CCK by the duodenum, and the availability of glucose and other nutrients to the cells. **308**
5. Appetite depends partly on the availability of glucose and other nutrients to the cells. The hormone insulin increases the entry of glucose to the cells, including cells that store nutrients for future use. Glucagon mobilizes stored fuel and converts it to glucose in the blood. Thus, the combined influence of insulin and glucagon determines how much glucose is available at any time. **309**
6. Constantly high levels of insulin, as in animals preparing for hibernation, lead to constant hunger because the food is going into storage instead of going to cells that need it. Constant low levels of insulin, as in diabetes, also leads to constant hunger, because the glucose is excreted instead of entering the cells. **309**
7. Fat cells produce a peptide called leptin that provides the brain with a signal about weight and thereby corrects day-to-day errors in the amount of feeding. Low levels of leptin increase hunger more effectively than high levels decrease it. **310**
8. The arcuate nucleus of the hypothalamus receives signals of both hunger and satiety. Good-tasting foods and the transmitter ghrelin stimulate neurons that promote hunger. Glucose, insulin, leptin, and CCK stimulate neurons that promote satiety. **311**
9. Axons from the two kinds of neurons in the arcuate nucleus send competing messages to the paraventricular nucleus, releasing transmitters that inhibit or excite the paraventricular nucleus. Cells in the paraventricular nucleus inhibit the lateral nucleus of the hypothalamus. Hunger signals increase feeding by inhibiting the inhibition from the paraventricular nucleus. **312**
10. The lateral nucleus of the hypothalamus facilitates feeding by axons that enhance taste responses elsewhere in the brain and increase the release of insulin and digestive juices. **312**
11. The ventromedial nucleus of the hypothalamus and the axons passing by it influence eating by regulating stomach emptying time and insulin secretion. Animals with damage in this area eat more frequently than normal because they store much of each meal as fat and then fail to mobilize their stored fats for current use. **313**
12. Obesity is partly under genetic control. Syndromal obesity occurs if a gene leads to both obesity and other medical problems. Monogenic obesity results from a single gene that does not impair other body functions. Common obesity is influenced by many genes, as well as environmental factors. **315**
13. Bulimia nervosa is characterized by alternation between undereating and overeating. It has been compared to addictive behaviors. **316**
14. Anorexia nervosa is characterized by refusal to eat enough to maintain a healthy weight. Antidepressant treatments are seldom effective. The increased physical activity associated with anorexia appears to be motivated by temperature regulation. **317**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

Anorexia nervosa **317**
arcuate nucleus **311**
Bulimia nervosa **316**
cholecystokinin (CCK) **308**
duodenum **308**
ghrelin **312**

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glucagon **309**
insulin **309**
lactase **306**
lactose **306**
lateral hypothalamus **312**
leptin **310**
melanocortins **312**
sham-feeding **308**
Type 1 diabetes **310**
Type 2 diabetes **310**
vagus nerve **308**
ventromedial hypothalamus (VMH) **313**

Thought Question

For most people, insulin levels tend to be higher during the day than at night. Use this fact to explain why people grow hungry a few hours after a daytime meal but not so quickly at night.

Stop & Check Answers

12. African groups domesticated cattle at different times and independently evolved genes for digesting lactose.

13. Animals that sham-feed do not become satiated, regardless of how much they taste.

14. If a cuff is attached to the junction between the stomach and duodenum so that food cannot leave the stomach, an animal becomes satiated when the stomach is full.

15. When the duodenum is distended, it releases CCK, which closes the sphincter muscle between the stomach and duodenum, increasing the rate at which the stomach distends. Also, neural signals from the intestines cause cells in the hypothalamus to release a shorter version of CCK as a neuromodulator.

16. Those with very low levels, as in type 1 diabetes, cannot get glucose to enter their cells, and therefore, they are constantly hungry. Those with constantly high levels deposit much of their glucose into fat and glycogen, so within a short time after a meal, the supply of blood glucose drops.

17. Those mice fail to produce leptin. Nearly all overweight people produce enough leptin, and extra leptin only weakly suppresses appetite.

18. Insulin, CCK, and leptin increase satiety. Ghrelin increases hunger.

19. The output inhibits the paraventricular nucleus, and thereby stops it from inhibiting the lateral hypothalamus.

20. Melanocortins excite neurons in the paraventricular nucleus, and therefore decrease appetite.

21. Activity of the lateral hypothalamus improves taste, enhances cortical responses to food, and increases secretions of digestive juices.

22. Animals with damage to the ventromedial hypothalamus eat more frequent meals. Animals with damage to the paraventricular nucleus of the hypothalamus eat larger meals.

23. They shifted from a diet of local plants that were seasonally available to a calorie-rich diet that is available throughout the year.

24. Some of them contain unapproved chemicals not listed on the label.

25. Rats that alternate between food deprivation and a very sweet diet gradually eat more and more, and they react to deprivation of the sweet diet with head shaking and teeth chattering, like the symptoms of morphine withdrawal.

26. If the room is cool and the rats have access to a running wheel, they will exercise enough to keep warm, which causes them to lose weight.

Module 9.3 | End-of-Module Quiz

1. Most Southeast Asians limit their consumption of milk because of what?
- **a.** Their enzymes
- **b.** Their taste buds
- **c.** Their surface-to-volume ratio
- **d.** Their olfactory sensitivity

2. How does eating more carbohydrates increase tryptophan in the brain?
- **a.** Digesting carbohydrates increases blood pressure.
- **b.** Eating carbohydrates increases the appetite for eating proteins.
- **c.** The brain converts carbohydrates into tryptophan.
- **d.** Increased insulin removes phenylalanine from circulation.

3. When food distends the duodenum, the duodenum releases the hormone CCK. By what *peripheral* mechanism (outside the brain) does it increase satiety?
- **a.** CCK increases stomach contractions.
- **b.** CCK tightens the sphincter muscle between the stomach and the duodenum.
- **c.** CCK increases the ability of nutrients to enter cells.
- **d.** CCK decreases metabolic rate.

4. What is the effect of CCK on appetite?
- **a.** It increases appetite.
- **b.** It limits the size of a meal.
- **c.** It decreases the frequency of meals.
- **d.** It produces nausea.

5. Which of these does insulin do?
- **a.** It helps the intestines digest glucose.
- **b.** It helps glucose enter cells.
- **c.** It converts glucose into glutamate.
- **d.** It converts stored fats into glucose.

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6. What causes Type 2 diabetes?

- **a.** The pituitary gland decreases its secretion of releasing hormones.
- **b.** The pancreas stops making or releasing insulin.
- **c.** Cells become insensitive to the effects of insulin.
- **d.** The intestines decrease their ability to absorb glucose.

7. Which part of the body secretes leptin?

- **a.** The duodenum
- **b.** The fat cells
- **c.** The stomach
- **d.** The liver

8. How do the "hunger" cells of the arcuate nucleus increase eating?

- **a.** By inhibiting the paraventricular nucleus
- **b.** By stimulating the lateral hypothalamus
- **c.** By stimulating the ventromedial hypothalamus
- **d.** By inhibiting the sphincter muscle between the stomach and the duodenum

9. Which part of the body secretes ghrelin?

- **a.** The duodenum
- **b.** The fat cells
- **c.** The stomach
- **d.** The liver

10. What do variants in the FTO gene do?

- **a.** They increase the probability of bulimia nervosa.
- **b.** They alter the metabolism of lactose.
- **c.** They produce monogenetic obesity.
- **d.** They increase the probability of weight gain.

11. How has the prevalence of obesity changed since the availability of high-fructose corn syrup and artificially sweetened diet beverages?

- **a.** Each of them helped lower the prevalence of obesity.
- **b.** High-fructose corn syrup helped lower obesity rates, but diet drinks did not.
- **c.** Diet drinks helped lower obesity rates, but high-fructose corn syrup did not.
- **d.** The prevalence of obesity has increased after the availability of both of them.

12. The drug that is most effective for weight control binds to receptors for what chemical?

- **a.** Dopamine
- **b.** Insulin
- **c.** Serotonin
- **d.** Glucagon-like protein 1

13. Bulimia nervosa has been compared to which of the following?

- **a.** Borderline personality disorder
- **b.** Paranoid schizophrenia
- **c.** Drug addiction
- **d.** Fear of heights

14. Temperature regulation is a likely explanation for which aspect of anorexia nervosa?

- **a.** Higher prevalence in women than men
- **b.** Increased exercise
- **c.** Fear of becoming fat
- **d.** Age of onset

Answers: 1a, 2d, 3b, 4b, 5b, 6c, 7b, 8a, 9c, 10d, 11d, 12d, 13c, 14b.

Suggestions for Further Reading

Allen, J. S. (2012). *The omnivorous mind: Our evolving relationship with food.* Cambridge, MA: Harvard University Press. A discussion of all the ways eating affects our lives.

Gisolfi, C. V., and Mora, F. (2000). *The hot brain: Survival, temperature, and the human body*. Cambridge, MA: MIT Press. Discusses research on temperature regulation.

Chapter 10

Humans may be the only species that plans parenthood, but all species have a strong biological drive that leads to parenthood.

(David Merron Photography/Moment/Getty Images)

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Reproductive Behaviors

Chapter Outline

Module 10.1

Sex and Hormones

Evolutionary Interpretations of Male–Female Differences
Genes in Sexual Development
Organizing Effects of Sex Hormones
Activating Effects of Sex Hormones
Parental Behavior
In Closing: Reproductive Behaviors and Motivations

Module 10.2

Variations in Sexual Behavior

Gender Identity and Gender-Differentiated Behaviors
Sexual Orientation
In Closing: We Are Not All the Same

Learning Objectives

After studying this chapter, you should be able to:

1. Evaluate possible evolutionary explanations of men's and women's sexual behaviors.
2. Describe the role of the SRY gene in mammalian sexual development.
3. Explain the role of testosterone in the development of genital anatomy.
4. Distinguish between organizing and activating effects of hormones.
5. Explain why the degree of masculinization or feminization of brain anatomy varies among brain areas for a given individual.
6. Describe how hormones and experiences influence parental behavior.
7. Explain the relevance of intersex people for understanding the role of hormones in the development of sex-typed behaviors.
8. Discuss possible biological influences on the development of sexual orientation.

Why do we enjoy sex? We evolved to enjoy it because it leads to reproduction, which passes on genes. You evolved from a long line of ancestors who engaged in sexual activity at least once.

But why did we evolve to reproduce sexually instead of individually? In some species of reptiles, a female sometimes reproduces *asexually*—that is, using only her own genes and none from a male (Booth et al., 2011). Asexual reproduction would produce offspring exactly like yourself, instead of only half like yourself. What advantage does sex provide?

You might suggest the advantage of having a partner while you rear children. In humans, that kind of cooperation can be important, but many species reproduce sexually even though the male doesn't help at all with the young, and in some fish species, neither sex cares for the young—they just release their sperm and eggs in the same place and then depart.

Biologists' explanation is that sexual reproduction increases variation and thereby enables evolutionary adaptations to a changing environment, especially new viruses and parasites (Morran et al., 2011). Certain invertebrates reproduce sexually when they live in a complex and changing environment but reproduce without sex when they live in a constant environment (Becks and Agrawal, 2010).

Sex also minimizes disadvantageous genes. Suppose you have two new mutations, one helpful and one harmful. If you reproduced asexually, all your offspring would have both the good and the bad mutation. But with sexual reproduction, some will get the good without the bad (McDonald et al., 2016). Also, if you have a disadvantageous mutation in one gene and your mate has a disadvantageous mutation in a different gene, your children might get normal copies of both genes. In this chapter, we consider questions about the biology of sexual reproduction.

Module 10.1

Sex and Hormones

Learning Objectives

After studying this module, you should be able to:

1. Evaluate possible evolutionary explanations of men's and women's sexual behaviors.
2. Describe the role of the SRY gene in mammalian sexual development.
3. Explain the role of testosterone in the development of genital anatomy.
4. Distinguish between organizing and activating effects of hormones.
5. Explain why the degree of masculinization or feminization of brain anatomy varies among brain areas for a given individual.
6. Describe how hormones and experiences influence parental behavior.

Men and women differ on average in many aspects of behavior. Many of those differences are so small, so variable, or so culture-dependent that they do not call for a biological explanation. In other cases, however, explanations in terms of genetics or hormones are worth considering. In this module we deal with the consequences of being biologically male or female. The second module discusses gender identity and sexual orientation.

Evolutionary Interpretations of Male–Female Differences

According to Charles Darwin's theory of evolution by natural selection, individuals whose genes help them survive will produce more offspring, and therefore those genes will spread in the population. A second part of his theory was **sexual selection**: Genes that increase an individual's probability of mating, or probable number of surviving offspring, will also spread in the population. For example, males' large antlers in some deer species are important for attracting mates. In many bird species, the male's brightly colored feathers are important for attracting females. In a few species, such as phalaropes, the female lays eggs and then deserts them, leaving the male to attend to them. In those species, the female's bright colors help her attract a male.

In humans, too, some male–female differences may be results of sexual selection. Let's consider some examples that evolutionary psychologists have proposed (Buss, 2000).

Panu Ruangjan/Shutterstock.com

A female phalarope is brilliantly colored, and the male is drabber. The female lays eggs and deserts the nest, leaving the male to attend to it. (**Source:** A. Morris/Vireo: The Academy of Natural Sciences)

Interest in Multiple Mates

Across cultures, more males than females seek opportunities for multiple sexual partners. Why? From the evolutionary standpoint of spreading one's genes, males can succeed by either of two strategies (Gangestad and Simpson, 2000): be loyal to one woman and devote your energies to helping her and her babies, or mate with many women and hope that some of them can raise your babies without your help. No one needs to be conscious of these strategies. The idea is that males in the past who acted in either of these ways propagated their genes.

In contrast, a woman can have no more than one pregnancy per 9 months, regardless of her number of sex partners. A woman can sometimes gain from having multiple sex partners (Hrdy, 2000). If her partner is infertile, then mating with another man could be her only way of reproducing. An extra sexual partner may provide support to her and her children. In addition, she has the possibility of "trading up," abandoning her first mate for a better one. Still, men potentially have more to gain from multiple sex partners than women do. Researchers have no direct evidence that genes influence people's preferences for one mate or many. However, males of most other mammalian species also seek multiple mates, and their behavior is almost certainly genetically based.

Differences in Jealousy

Sexual jealousy varies among cultures. Some cultures tolerate sexual infidelity by husbands but not wives, and some tolerate it by both or neither, but no known society considers infidelity more acceptable for women than for men. An evolutionary standpoint suggests this explanation: For a male to pass on his genes, he should be sure that the children he supports are his own, and an unfaithful female threatens that certainty. Because a female knows that any children she bears are her own, she does not have that worry, although she might worry if her partner starts supporting some other female's children, instead of hers. David Buss and colleagues surveyed heterosexual young people and found, as they predicted, that men said they would be more upset if their partner became sexually intimate with another man than if she became emotionally intimate with him. Women reported that they would be more upset if their partner became emotionally intimate with another woman than if he had sex with her (Buss et al., 1992). Several similar studies have found similar results, although the size of the effect varies among cultures (Sagarin et al., 2012; Scelza et al., 2020). The difference is not huge, because both men and women are upset about either sexual or emotional infidelity. An evolutionary explanation is plausible for the general trend. However, as was the case with preferences for multiple partners, we have no direct evidence of any gene that controls jealousy. Mate-guarding or sexual jealousy occurs in many other mammals, but it is not universal. Bonobos, tied with chimpanzees for being our closest relatives, display no indication of sexual exclusivity.

All this discussion is an attempt to explain how people usually do act, not to say how they should act. The needs of life in a civilized society sometimes conflict with biological tendencies.

Mate Preferences

Almost everyone, regardless of gender or sexual orientation, prefers a romantic partner who is healthy, intelligent, honest, kind, and physically attractive, with religious and political beliefs similar to one's own. A difference is that women are more likely than men to prefer a mate who is likely to be a good provider (Buss, 2000; Conroy-Beam et al., 2015; Walter et al., 2020). Evolutionary theorists emphasize that while a woman is pregnant or taking care of a small child, she may need help with food and other requirements, and therefore evolution would have favored a tendency for women to seek good providers.

This evolutionary explanation is less persuasive than in the previous two examples. The tendency for females to prefer good providers is mostly limited to humans, because most male mammals provide little help to pregnant or nursing females. Chimpanzees and bonobos do, sometimes. If the preference for a good provider is a product of evolution, it had to be relatively recent, as evolution goes. Furthermore, in countries where women have good economic opportunities of their own, their preference for a wealthy male is substantially weaker (Walter et al., 2020).

Stop & Check

1. What evolutionary advantage is suggested for why men tend to be more jealous of a woman's sexual infidelity?

See page 337 for the answer.

Genes in Sexual Development

For mammals, sexual differentiation begins with the genes. Females have two X chromosomes, whereas males have an X and a Y chromosome. (The mechanisms of sex determination differ for birds, reptiles, and fish.) Biologists used to believe that the chromosomes determine sexual differentiation entirely through hormones. We will get to the hormones, but let's start with effects of genes themselves.

A few genes on the Y chromosome are active in the brain, at least one gene on the X chromosome is active only in the female brain (Arnold, 2004, 2009; Carruth et al., 2002; Vawter et al., 2004), and several genes on the X chromosome produce larger effects in females (Raznahan and Disteche, 2021). Because males have only one X chromosome, a recessive gene on the X chromosome shows its effects more often in males than in females, including some effects that cause intellectual deficiencies (Mallard et al., 2021). The X and Y chromosomes also have sites that alter the expression of genes on other chromosomes (Lemos et al., 2008). Furthermore, prenatal testosterone has a greater effect on genetic males than on genetic females (Balthazart, 2020).

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Some people have chromosome patterns that are neither XX nor XY. **Turner syndrome** is characterized by an XO pattern—an X chromosome and no second sex chromosome, or just part of a second X chromosome, or one X in some cells and two Xs in others. The result is a typical feminine appearance, and almost always self-identification as female, but ovaries that secrete less than average amounts of sex hormones. Most women with Turner syndrome are shorter than average and few have successful pregnancies without medical help. Psychologically, much variation occurs. A common pattern is below average math and visuospatial skills, but normal or above-average performance on certain aspects of language (Hutaff-Lee et al., 2019; Temple and Shephard, 2012). Social difficulties and depression are somewhat more common than in other women.

Klinefelter syndrome is characterized by an XXY pattern, or less commonly XXYY or XXXY. The appearance is masculine, but most individuals are infertile. The testes are smaller than average, and some breast growth is common at puberty. Learning difficulties are common, especially with language and problem solving, and mental health problems are elevated (Bird and Hurren, 2016; Fjermestad et al., 2020).

At one time, theorists expected that men with an XYY chromosome pattern would be prone to violent behavior. After all, if one Y chromosome increases aggressiveness, two should be especially risky. Research has not supported that expectation. The extra Y chromosome correlates with being slightly taller than average, and perhaps an increased probability of cognitive impairment (Re and Birkhoff, 2015).

One research problem is that all these chromosomal anomalies are more likely to be noticed in people who are brought to medical attention because of physical or behavioral problems. It is possible that the published research overestimates the differences.

Stop & Check

2. According to the published data, what do Turner syndrome, Klinefelter syndrome, and XYY conditions have in common?

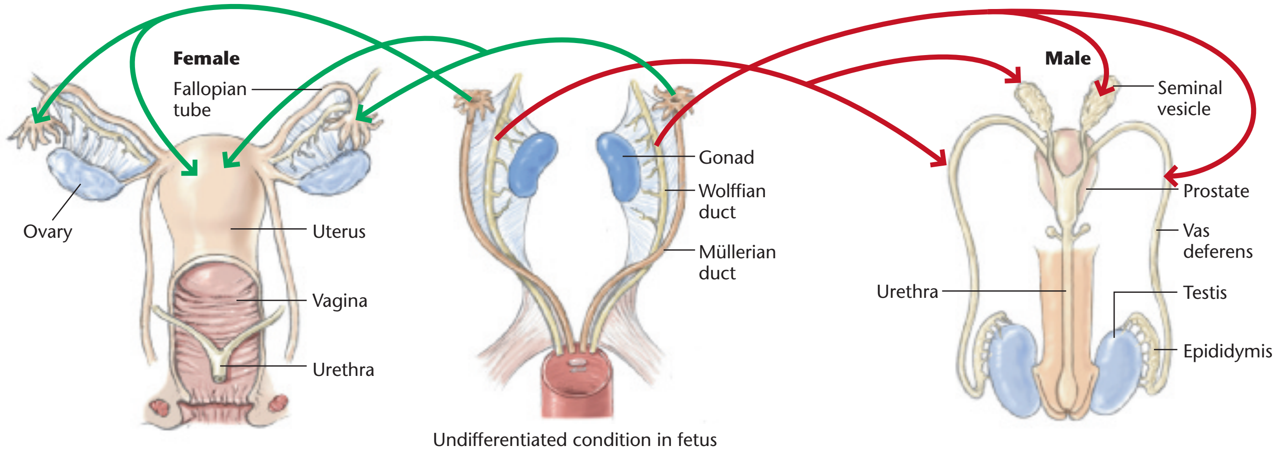
See page 337 for the answer.

Organizing Effects of Sex Hormones

Male and female mammals have the same anatomy during an early stage of prenatal development. Both have **Müllerian ducts** (precursors to female internal structures) and **Wolffian ducts** (precursors to male internal structures), and gonads that look alike. A little later in biological males, the **SRY gene** (Sex-determining Region on the Y chromosome) causes those undifferentiated gonads to develop into **testes**, the sperm-producing organs. The testes produce **androgens** (male-typical hormones) that increase the growth of the testes, causing them to produce still more androgens. That positive feedback cannot go on forever, but it continues for a while. Androgens cause the Wolffian ducts to develop into *seminal vesicles* (structures that store semen) and the *vas deferens* (a duct from the testis into the penis). The testes also produce *Müllerian-inhibiting hormone* (*MIH*) that causes the Müllerian ducts to degenerate. The result is a penis and scrotum. Because biological females do not have the SRY gene, the gonads develop into **ovaries** instead of testes, the Wolffian ducts degenerate, and the Müllerian ducts mature into oviducts, uterus, and the upper vagina. The structure that would have developed into a penis develops into a clitoris instead. Figure 10.1 depicts how the

Figure 10.1 Differentiation of human genitals

We begin life with undifferentiated structures, shown in the center. The gonad of the fetus, shown in blue, develops into either the ovaries, as shown on the left, or the testes, as shown on the right. The Müllerian ducts of the fetus develop into a female's uterus, oviducts, and the upper part of the vagina. The Wolffian ducts of the fetus develop into a male's seminal vesicles and vas deferens.



(**Source:** Based on Netter, 1983)

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primitive unisex structures develop the male or female pattern. Variations are possible, as we consider later.

The males' testes produce more androgens than **estrogens** (hormones that are more abundant in females), whereas the females' ovaries produce more estrogens than androgens. The adrenal glands also produce smaller amounts of both androgens and estrogens, and the brain produces estrogens, which aid in memory and other cognitive functions (Arevalo et al., 2015). Androgens and estrogens have similar effects in some ways and different effects in others. They are **steroid hormones**, containing four carbon rings, as in Figure 10.2. Androgens and estrogens are categories of chemicals. Androgens include **testosterone**, and estrogens include **estradiol**. **Progesterone**, another predominantly female hormone, prepares the uterus for the implantation of a fertilized ovum and promotes the maintenance of pregnancy.

Steroids exert their effects in three ways (Nadal et al., 2001; Taxier et al., 2020). They bind to receptors on the membrane, they enter cells and activate certain proteins, and they bind to chromosomes to activate or inactivate certain genes (Figure 10.3).

If we injected estrogens into adult males and androgens into adult females, could we make males act like females or females act like males? The results depend on the species and the duration of exposure, but in general the behavioral effects are unimpressive (Henley et al., 2011). Hormones early in life have much stronger effects.

Biologists distinguish between the organizing and activating effects of sex hormones. **Organizing effects** are long-lasting. During a **sensitive period** in early development, which is the first trimester of pregnancy for humans, sex hormones determine whether the body develops female or male genitals (Money and Ehrhardt, 1972). A bit later, they alter certain aspects of brain development. Sex hormones produce additional organizing effects at puberty. The surge of hormones at puberty produces breast development in females, facial hair and penis growth in males, and changes in voice (Ahmed et al., 2008; Vijayakumar et al., 2021). The anatomical changes at puberty persist throughout life, even after the concentration of sex hormones declines.

Activating effects are temporary, continuing only while a hormone is present. For example, current hormone levels influence the degree of sex drive. The burst of hormones during pregnancy produces temporary

Figure 10.2 Steroid hormones

Note the chemical similarity between testosterone and estradiol.

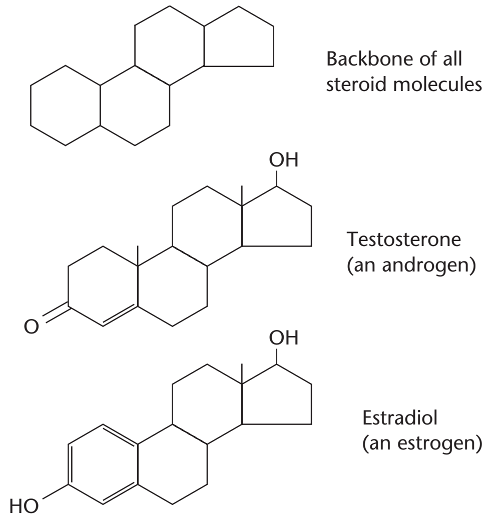
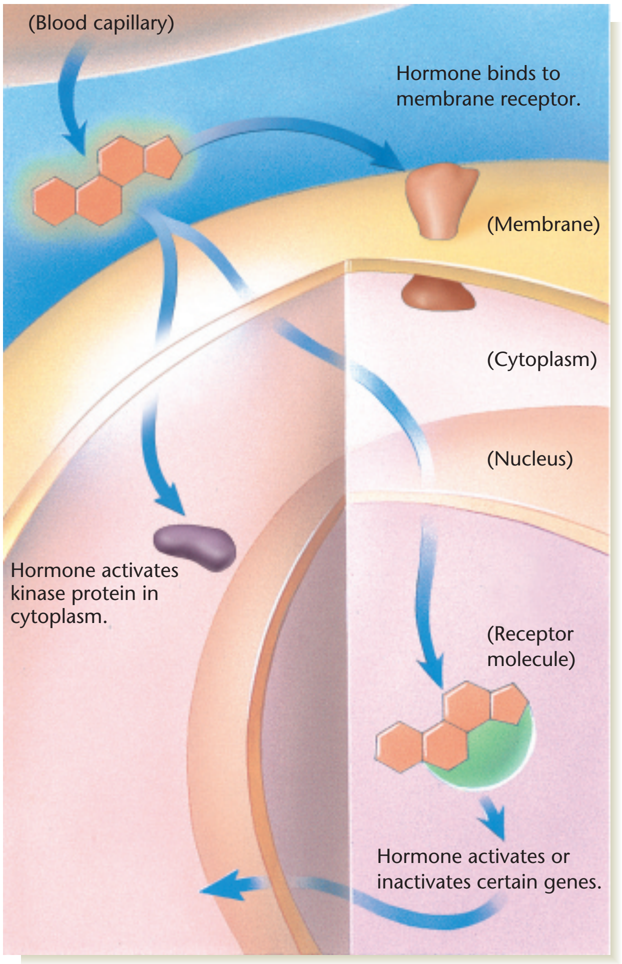


Figure 10.3 Routes of action for steroid hormones

Steroid hormones such as estrogens and androgens bind to membrane receptors, activate proteins in the cytoplasm, and activate or inactivate certain genes.


(Blood capillary)
Hormone binds to membrane receptor.
(Membrane)
(Cytoplasm)
(Nucleus)
Hormone activates kinase protein in cytoplasm.
(Receptor molecule)
Hormone activates or inactivates certain genes.

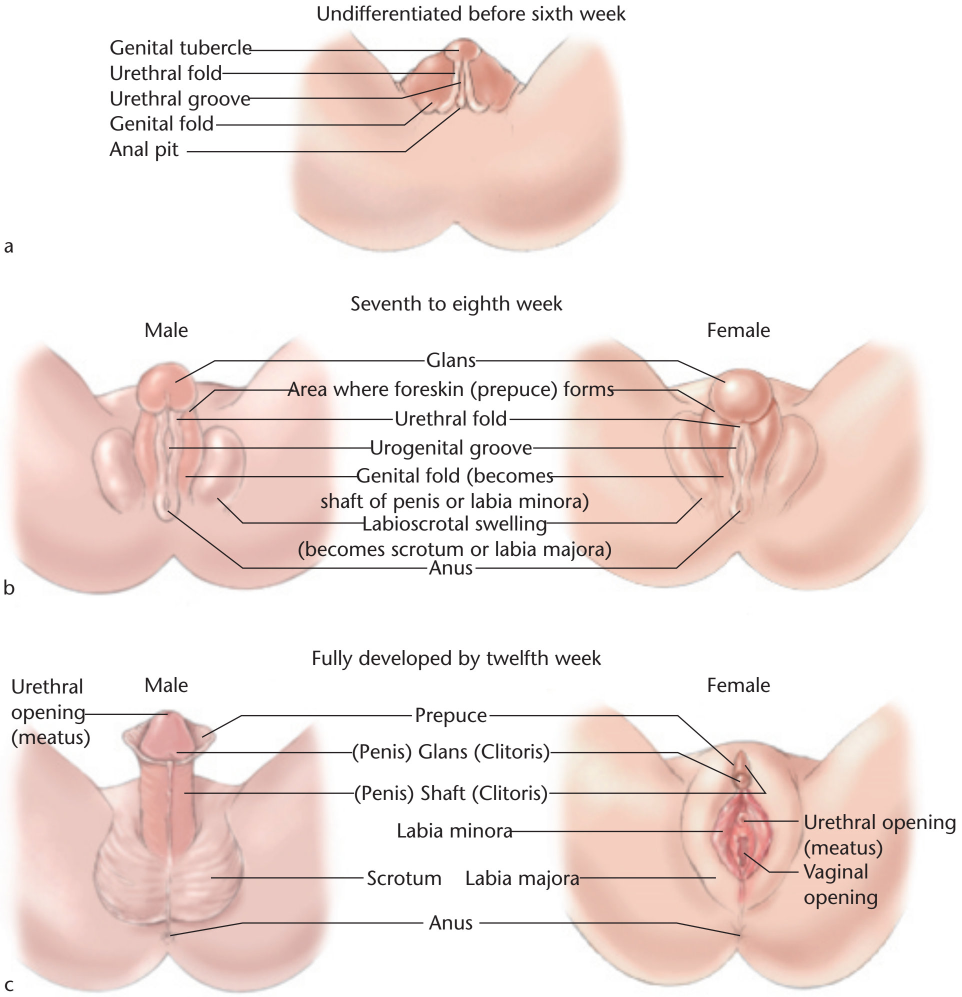
(**Source:** Revised from Starr and Taggart, 1989) effects on emotional arousal, defensive behaviors, and cognition (Agrati et al., 2011; Workman et al., 2012). Organizing effects set the stage for activating effects. For example, organizing effects set up the female hypothalamus such that later hormones can activate the menstrual cycle. The distinction between organizing and activating effects is not absolute, as hormones often produce a combination of temporary and longer-lasting effects (Arnold and Breedlove, 1985; C. L. Williams, 1986).

Let's focus on the organizing effects during the early sensitive period, when hormones determine whether an embryo develops a male or female anatomy. You might imagine that testosterone produces male anatomy and estradiol produces female anatomy. No. In mammals, differentiation of the external genitals depends on testosterone. A high level of testosterone causes the external genitals to develop the male pattern, and a low level leads to the female pattern. Estradiol is essential for proper development of a female's uterus and other internal organs, but it has little effect on the external genitals.

At first, the external genitals of males and females look the same, as illustrated in Figure 10.4. As a male's developing testes secrete testosterone, enzymes convert it to dihydrotestosterone, which is more effective for penis growth. If the dihydrotestosterone level is high enough, the tiny genital tubercle grows and develops into a penis. If the level is low, the tubercle becomes a clitoris. Similarly, depending

Figure 10.4 Development of the Human Genitals

The initial appearance is the same for all. Depending on the level of testosterone and its metabolite, dihydrotestosterone, the embryo develops either the male pattern or the female pattern.


Undifferentiated before sixth week
Genital tubercle
Urethral fold
Urethral groove
Genital fold
Anal pit
a
Seventh to eighth week
Male
Female
Glans
Area where foreskin (prepuce) forms
Urethral fold
Urogenital groove
Genital fold (becomes shaft of penis or labia minora)
Labioscrotal swelling (becomes scrotum or labia majora)
Anus
b
Fully developed by twelfth week
Urethral opening (meatus)
Male
Female
Prepuce
(Penis) Glans (Clitoris)
(Penis) Shaft (Clitoris)
Labia minora
Scrotum
Labia majora
Urethral opening (meatus)
Vaginal opening
Anus
c

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on levels of testosterone and dihydrotestosterone, the embryo develops either a scrotum, characteristic of males, or labia, characteristic of females.

Much of the research exploring sexual development has been in rodents. In rats, testosterone begins masculinizing the external genitals during the last several days of pregnancy and first few days after birth and then continues masculinizing them at a declining rate for the next month (Bloch and Mills, 1995; Bloch et al., 1995; Davis et al., 1995; Rhees et al., 1990). A female rat that is injected with testosterone during this period is partly masculinized, just as if her own body had produced the testosterone (Ward and Ward, 1985). Her clitoris grows larger than normal, and her behavior is partly masculinized. She approaches sexually receptive females (Woodson and Balleine, 2002), mounts them, and makes copulatory thrusting movements rather than arching her back and allowing males to mount her. In short, early testosterone promotes the male pattern and inhibits the female pattern (Gorski, 1985; Wilson et al., 1981).

Injecting a genetic male with estrogens during early development produces little effect on his external anatomy, but a genetic male that lacks androgens or androgen receptors develops a female-typical pattern of anatomy and behavior. That outcome could result from castration (removal of the testes) or a genetic deficiency of androgen receptors. Prenatal exposure to drugs that interfere with androgen response can impair male development to various degrees, depending on the type of drug and the amount of exposure (Hull et al., 1984). Although estradiol does not significantly alter a male's external anatomy, estradiol and related compounds do produce abnormalities of the prostate gland—the gland that produces a fluid that protects sperm cells when ejaculated during intercourse. Some of those estradiol-like compounds are now prevalent in the linings of plastic bottles and cans, so almost everyone has some exposure to them (Timms et al., 2005).

Researchers used to say that nature's default setting is to make every mammal a female unless told to do otherwise. Add early testosterone and the individual becomes a male; otherwise, it develops as a female. That generalization applies only to external genital anatomy. A genetic female without estradiol early in life does not develop typical internal anatomy or sexual behavior, even if she is given estradiol injections as an adult (Bakker et al., 2002; Brock et al., 2011).

Stop & Check

3. What does the SRY gene do?
4. What would be the external genital appearance of a mammal exposed to high levels of both androgens and estrogens during early development?
5. What would be the external genital appearance of a mammal exposed to a low level of both androgens and estrogens in early development?

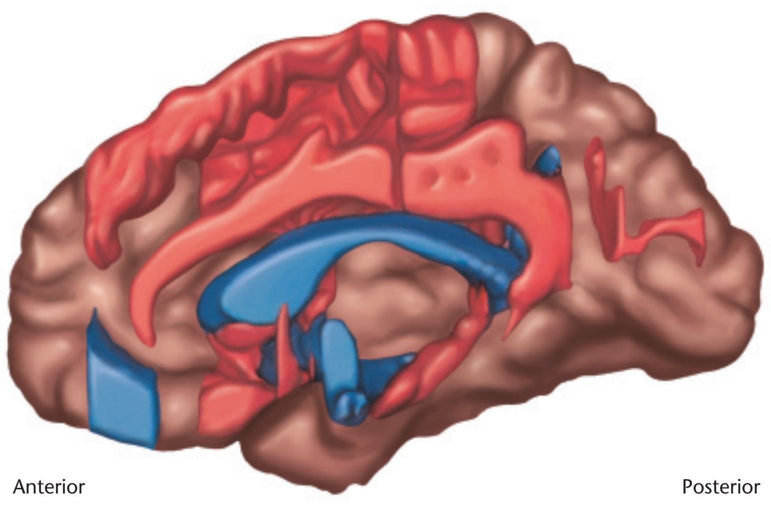
See page 337 for the answer.

Sex Differences in the Brain

The female hypothalamus generates a cyclic pattern of hormone release, as in the human menstrual cycle, whereas the male hypothalamus releases hormones more steadily. For the rest of the brain, male and female brains differ on average in many ways, although the differences are small, and definitely "on average," with a full overlap between the male and female distributions. Figure 10.5 shows which brain areas tend to form a larger percentage of the male brain or the female brain (Cahill, 2006). On average, females have stronger connections between the two hemispheres, and males have more connections within each hemisphere (McCarthy et al., 2017). Another difference is that female brains tend to age more slowly. That is, the metabolic rate in the brain declines more rapidly in males than in females (Goyal et al., 2019). You may sometimes hear someone point to a difference on average between male

Figure 10.5 Male and female brains

Areas in red are, on average, larger in women relative to the total mass of the brain. Areas in blue are, on average, larger in men relative to the total mass.



(**Source:** From Cahill, L. (2006). Why sex matters for neuroscience. *Nature Reviews Neuroscience, 7*, 477–484. Reprinted by permission of Macmillan Publishing Ltd.)

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Table 10.1 | Sexual Differentiation of the Hypothalamus

Hypothalamic Area	Male–Female Difference	Caused by
Medial preoptic area	More dendritic spines and synapses in males	Testosterone and estradiol increase production of prostaglandin E_2.
Ventromedial nucleus	More widely branched dendrites in males	Estradiol activates PI3 kinase, which increases glutamate release.
Arcuate nucleus and anteroventral periventricular nucleus	More dendritic spines and synapses in females	Estradiol increases GABA production, which acts on astrocytes to decrease dendritic branching.

and female brains and claim that it explains why men behave differently from women in some regard. Be skeptical of such claims, which are almost always speculative. The differences between male and female brains correlate only weakly with male–female behavioral differences (van Eijk et al., 2021),

What causes the brain differences? In rats during early development, a male's testosterone enters cells of the hypothalamus, where an enzyme converts much of it to estradiol, which exerts *masculinizing* effects at this time. (You're right, that is confusing.) In rodents, the infant blood contains high levels of alpha-fetoprotein, a chemical that prevents estradiol from entering cells (Gorski, 1980; MacLusky & Naftolin, 1981). Therefore, the female brain is not exposed to estradiol during early development. The male brain is exposed to both testosterone and estradiol.

Research by Margaret McCarthy and her colleagues has found that the mechanisms differ from one brain area to another. In the medial preoptic area, both testosterone itself and its conversion to estradiol increase the production of a chemical called prostaglandin E_2, which leads to an increase in microglia, dendritic spines, and synapses (Lenz et al., 2013; Nugent et al., 2015). In another part of the preoptic area (the "anteroventral periventricular nucleus of the preoptic area," which is quite a mouthful), estradiol and testosterone combine to increase cell death in males, leaving this area larger in females (McCarthy et al., 2017). In part of the ventromedial hypothalamus, estradiol activates an enzyme called PI3 kinase that increases glutamate release, and thereby causes postsynaptic neurons to increase their dendritic branching (Schwarz et al., 2008). In the arcuate nucleus and the anteroventral periventricular nucleus, estradiol increases GABA production, which acts on astrocytes to decrease dendritic spines. The result for males is shrinkage of these areas that are important for female sexual behavior. These areas remain larger in females because of their relatively low levels of brain estradiol during early development (McCarthy, 2010; McCarthy & Arnold, 2011). Table 10.1 summarizes these mechanisms. In humans and other primates, testosterone acts on the hypothalamus directly instead of by conversion to estradiol, but the final mechanism in terms of prostaglandins, PI3 kinase, and so forth appear to be the same as in rodents.

Now, why is all this important? Because the mechanisms differ from one brain area to another, it is possible for one area to become more masculinized or more feminized than another. In many brain areas, the male–female differences depend on not only testosterone and estradiol but also the immune system (McCarthy, 2020) and genes that are more active in one sex or the other (Reinius et al., 2008). Because genes vary, and so do epigenetic changes, few people have a brain that is male-typical or female-typical in all regards. Almost anyone's brain is a mosaic of male-typical, female-typical, and neutral areas (Joel et al., 2015). Brain anatomy is "nonbinary." And just as it is true that brains are a mosaic of male-typical and female-typical areas, most people have a mixture of male-typical and female-typical interests, attitudes, and activities. One study found that mental health tended to be better among people whose brains were somewhere near the middle of the continuum from extremely male-typical to extremely female-typical (Zhang et al., 2021).

Stop & Check

6. How would the external genitals appear on a genetic female rat that lacked alpha-fetoprotein?
7. Why is any individual's brain more masculinized or feminized in some areas than others?

See page 337 for the answer.

Margaret McCarthy

In the past two decades, the range of neurobiological, psychological, and psychiatric endpoints found to differ between males and females has expanded beyond reproduction into every aspect of the healthy and diseased brain, and thereby demands our attention. (McCarthy, 2016)

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Sex Differences in Play

One of the larger male–female differences in behavior relates to play. The average difference between boys and girls in toy preference is bigger than the average difference between men and women in height (Hines, 2020). Boys more often choose to play with toy cars and trains, balls, guns, and roughhouse activities. Girls are more likely than boys to prefer calmer, cooperative play. Preferences tend to be consistent over time and similar across cultures. Children who show the most boy-typical play at age 3 usually show the greatest preference for boy-typical activities at age 13, and those with the most girl-typical play at 3 usually show the greatest preference for girl-typical activities at 13 (Golombok et al., 2012).

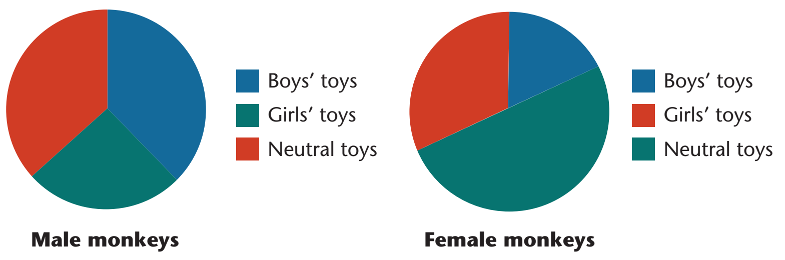
Socialization contributes to the pattern, as most parents give their sons and daughters different sets of toys, but socialization need not be the whole story. Indeed, it may be that parents give those toys because previous generations observed differences in boys' and girls' interests. Furthermore, rough-and-tumble play and impulsive behavior are typical of young males of many other species, caused by the way that prenatal androgens alter the amygdala (Darling et al., 2020; van Ryzin et al., 2019).

In two studies male monkeys played with balls and toy cars more than female monkeys did (Alexander and Hines, 2002; Hassett et al., 2008). Figure 10.6 summarizes the results from one of those studies. Monkeys' preferences were not strong as those of children, but it is noteworthy that male and female monkeys differed at all in their first encounters with these toys. Other studies found that prenatal injections of testosterone to female monkey fetuses led to increased masculine-type play after they were born. In those cases, the focus was on spontaneous, rough-and-tumble play rather than playing with toys, but the idea is similar (Wallen, 2005).

Back to humans: Researchers correlated chemicals in the mother's blood during pregnancy with the daughters' toy choices at age 3½. The girls who had been exposed to higher testosterone levels in prenatal life showed slightly elevated preferences for boys' toys (Hines et al., 2002). These girls were anatomically normal. A similar study measured testosterone in the amniotic fluid of 212 pregnant women and found a significant correlation with the male-typical play of their children 6 to 10 years later (Auyeung et al., 2009). Still another study measured testosterone levels in infants over the first 6 months and compared results to their toy choices at age 14 months. Girls with higher testosterone levels in early infancy spent more time than average playing with toy trains, compared to other girls. Boys with higher testosterone levels spent less time than other boys did playing with dolls (Lamminmäki et al., 2012).

Figure 10.6 Toy choices by male and female monkeys

Male monkeys spent more time than female monkeys did with "boys' toys."



(**Source:** Based on data from "Sex differences in response to children's toys in nonhuman primates (*Cercopithecus aethiops sabaeus*)," by G. M. Alexander and M. Hines, 2002, *Evolution and Human Behavior, 23*, 467–479.)

Stop & Check

8. What evidence links children's toy play to prenatal hormones?

See page 337 for the answer.

Activating Effects of Sex Hormones

At any time in life, current levels of testosterone or estradiol exert activating effects, temporarily modifying behavior. Behaviors can also influence hormonal secretions. For example, when doves court each other, each stage of their behavior initiates hormonal changes that alter the birds' readiness for the next sequence of behaviors (Erickson and Lehrman, 1964; Lehrman, 1964; Martinez-Vargas and Erickson, 1973).

In addition to the sex hormones, the pituitary hormone **oxytocin** is also important for reproductive behavior. Oxytocin stimulates contractions of the uterus during delivery of a baby, and it stimulates the mammary gland to release milk. Sexual pleasure releases oxytocin, especially at orgasm (Murphy et al., 1990). Oxytocin is responsible for the calmness and reduced anxiety after orgasm (Waldherr and Neumann, 2007).

Males

Androgens, essential for male sexual arousal, increase sensitivity in the penis and bind to receptors in the hypothalamus. Testosterone primes the medial preoptic area (MPOA) and other brain areas to release dopamine, which then increases male sex drive (Putnam et al., 2001). In rats, a few minutes of exposure to a receptive female also releases dopamine in the MPOA, producing the same effect (Zhang et al., 2021). Castrated male rats do not release dopamine in the presence of a receptive female, and they do not attempt to copulate (Hull et al., 1997).

In moderate concentrations, dopamine stimulates mostly type D_1 and D_5 receptors, which facilitate erection of the penis (Hull et al., 1992). In higher concentrations, dopamine stimulates type D_2 receptors, which lead to orgasm (Giuliani and Ferrari, 1996; Hull et al., 1992). Whereas dopamine stimulates sexual activity, the neurotransmitter serotonin inhibits it by blocking dopamine release (Hull et al., 1999). Many antidepressant drugs increase serotonin activity, and one of their side effects is decreased sexual arousal.

Levels of testosterone correlate positively with men's sexual arousal and their drive to seek sexual partners. Researchers found that, on average, married men and men living with a woman in a committed relationship have lower testosterone levels than unpaired men of the same age (M. McIntyre et al., 2006). Two explanations are possible: Marriage might decrease testosterone levels, because of decreased need to seek a sexual partner, or men with lower testosterone levels might be more likely to marry and remain faithful. Although both explanations may be correct to some extent, research supports the second explanation. Men with lower testosterone levels are more likely to marry, less likely to express a desire for additional partners after marriage, and less likely to have an illicit affair after marriage (Edelstein et al.; Klimas et al.; McIntyre et al., 2006; van Anders and Watson, 2006; van Anders et al., 2007).

Decreases in testosterone levels decrease male sexual activity. For example, castration decreases a man's sexual interest and activity. Anti-androgen drugs can help sex offenders reduce their sexual impulsiveness, after informed consent (Ly et al., 2020; Winder et al., 2014). However, low testosterone is not the usual basis for **impotence**, the inability to have an erection. The most common cause is impaired blood circulation, especially in older men. The drug sildenafil (Viagra) increases male sexual ability by increasing blood flow to the penis.

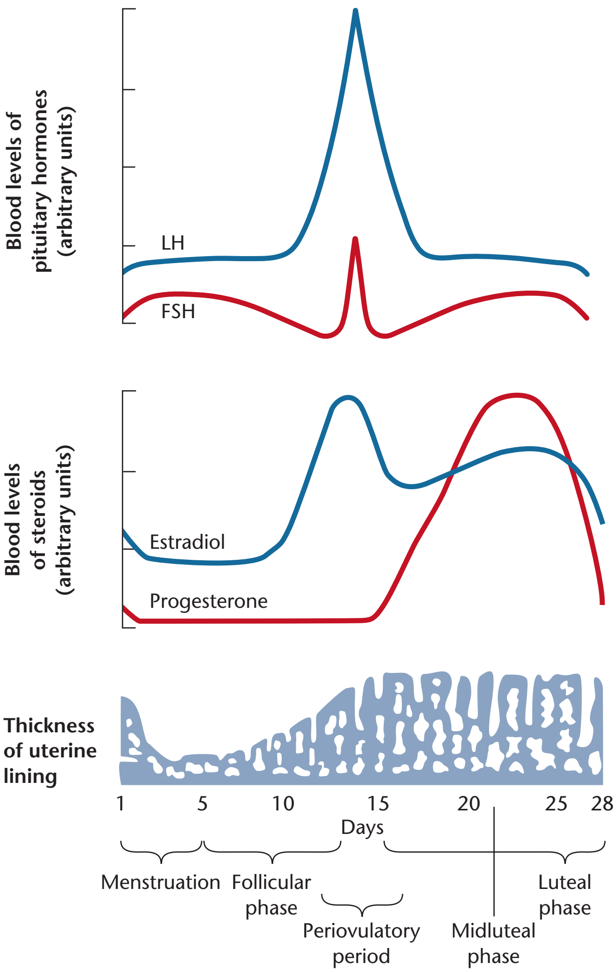
Stop & Check

9. By what mechanism does testosterone affect the hypothalamic areas responsible for sexual behavior?
10. Why do many antidepressant drugs decrease sexual arousal?

See page 337 for the answer.

Figure 10.7 Blood levels of four hormones during the human menstrual cycle

Note that estrogen and progesterone are both at high levels during the midluteal phase but drop sharply at menstruation.



Females

A woman's hypothalamus and pituitary interact with the ovaries to produce the **menstrual cycle**, a periodic variation in hormones and fertility over the course of about 28 days (Figure 10.7). After the end of a menstrual period, the anterior pituitary releases **follicle-stimulating hormone (FSH)**, which promotes the growth of a follicle in the ovary. The follicle nurtures the *ovum* (egg cell) and produces several types of estrogen, including estradiol. Toward the middle of the menstrual cycle, the follicle builds up more and more receptors to FSH, so that even though the concentration of FSH in the blood is decreasing, its effects on the follicle increase. Therefore, the follicle produces increasing amounts of estradiol. The increased estradiol increases release of FSH and a surge in the release of **luteinizing hormone (LH)** from the anterior pituitary (the top graph in Figure 10.7). FSH and LH combine to cause the follicle to release an ovum.

The remnant of the follicle (now called the *corpus luteum*) releases the hormone progesterone, which prepares the uterus for the implantation of a fertilized ovum. Progesterone also inhibits the further release of LH. During pregnancy, estradiol and progesterone levels continue to increase. Otherwise, both hormones decline (as shown in Figure 10.7), the lining of the uterus is cast off (menstruation), and the cycle begins again.

One consequence of high estradiol and progesterone levels during pregnancy is fluctuating activity at the serotonin 3 ($5HT_3$) receptor, which is responsible for nausea (Rupprecht et al., 2001). Pregnant women often experience

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nausea because of the heightened activity of that receptor. Figure 10.8 summarizes the interactions between the pituitary and the ovary. Increased sensitivity to nausea may be an evolved adaptation to minimize the risk of eating something harmful to the fetus.

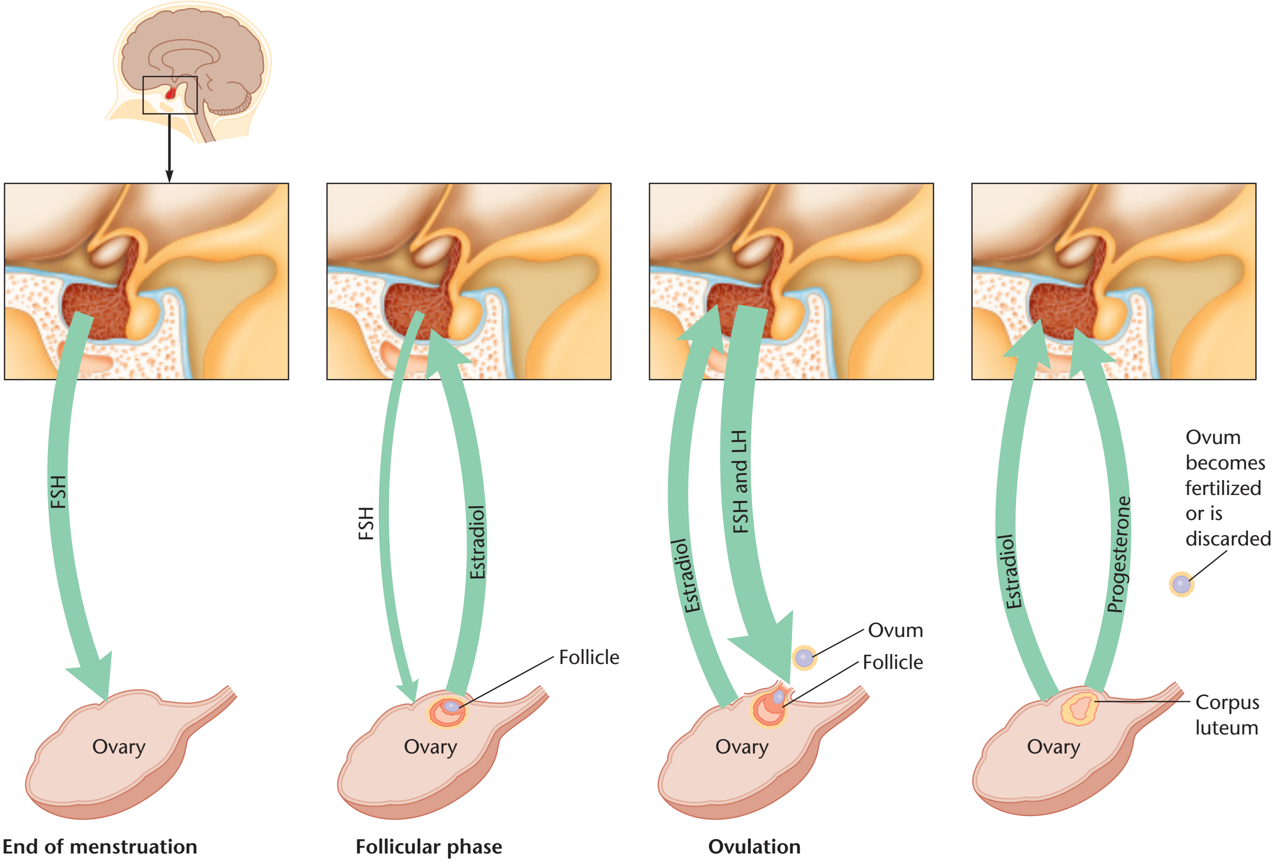
Birth control pills prevent pregnancy by interfering with the usual feedback cycle between the ovaries and the pituitary. The most widely used birth control pill, the *combination pill*, containing estrogen and progesterone, prevents the surge of FSH and LH that would otherwise release an ovum. The estrogen–progesterone combination also prevents an ovum from implanting in the uterus and thickens the mucus of the cervix, making it harder for a sperm to reach the ovum. Note, however, that birth control pills do not protect against sexually transmitted diseases. "Safe sex" means more than preventing pregnancy.

In female rats, a combination of estradiol and progesterone is the most effective combination for enhancing sexual behavior (Matuszewich et al., 2000). Estradiol increases the sensitivity of the *pudendal nerve*, which transmits tactile stimulation from the vagina and cervix to the brain (Komisaruk et al., 1972). Just as testosterone facilitates dopamine release in the medial preoptic area for males, estradiol does the same for females (Jennings and de Lecea, 2020). Estradiol appears to be essential to female sexual behavior in all mammals that have been tested.

At one time, the idea arose that human female sexual desire might depend on testosterone. The evidence contradicts that idea. Most women report a decrease in sexual desire after menopause, which decreases estradiol levels, or after surgical removal of the ovaries, which also reduces estradiol levels (Graziottin et al., 2009). Administering enough estradiol to return it to normal levels increases sexual desire. Testosterone does not increase a woman's sexual desire or pleasure except at levels beyond what occurs naturally in women (Cappelletti and Wallen, 2016). Furthermore, a study comparing women's increases and decreases of sexual interest from day to day across one or two months found that sexual desire correlated strongly with changes in levels of estradiol, not testosterone (Roney and Simmons, 2013). A woman's probability of sexual intercourse does not increase

Figure 10.8 Interactions between the pituitary and the ovary

FSH from the pituitary stimulates a follicle of the ovary to develop and produce estradiol, releasing a burst of FSH and LH from the pituitary. Those hormones cause the follicle to release its ovum and become a corpus luteum. The corpus luteum releases progesterone while the ovary releases estradiol.

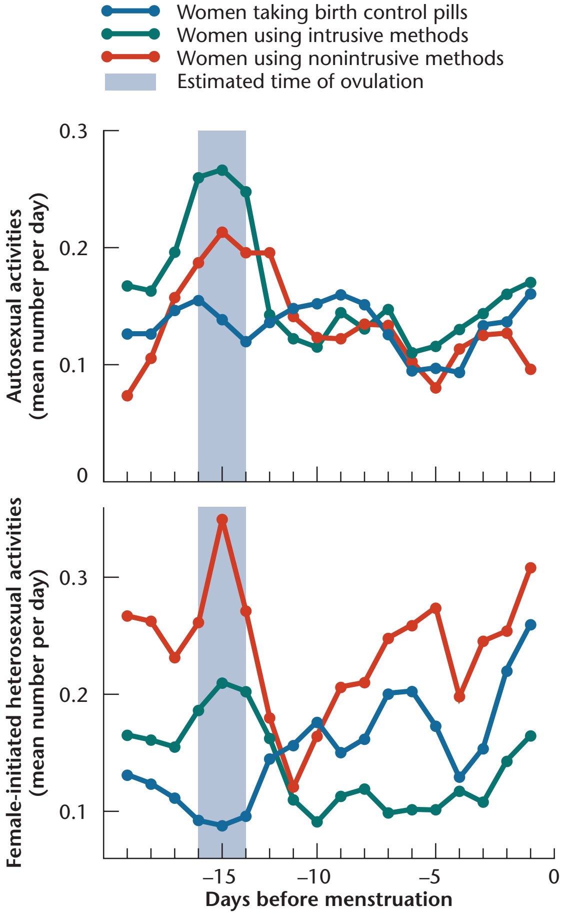


significantly during the **preovulatory period**—the days of her menstrual cycle when estradiol levels are highest. However, her probability of *initiating* sexual activity does increase at that time (Adams et al., 1978; Udry and Morris, 1968) (Figure 10.9). Also, unmarried women flirt more during this period than at other times (Cantú et al., 2014; Durante and Li, 2009).

Another study used a method that is, shall we say, uncommon among laboratory researchers. The researchers studied erotic lap dancers, who earn tips by dancing between a man's legs, rubbing up against his groin, while wearing, in most cases, just a bikini bottom. Lap dancers recorded the times of their menstrual periods and the amount of tip income they received each night. Lap dancers who were taking contraceptive pills (which keep hormone levels nearly constant) earned about the same amount from one day to another. Those not taking contraceptive pills received the largest tips during the periovulatory period (Miller et al., 2007). Presumably the women felt and acted sexier at this time.

Figure 10.9 Female-initiated sexual activities

The top graph shows autosexual activities (masturbation and sexual fantasies); the bottom graph shows female-initiated activities with a male partner. The shaded area is the time of greatest estradiol levels. "Intrusive" birth control methods are diaphragm, foam, and condom; "nonintrusive" methods are IUD and vasectomy. Women other than pill users initiate sex more often when their estrogen levels peak.



(**Source:** Adams et al., 1978)

Several studies have reported relationships between women's menstrual cycles and behaviors not directly related to sex, including women's preferences for highly masculine-looking faces, tendency to wear red, ability to recognize emotional expressions, and even religious beliefs and voting preferences. Attempts to replicate these findings have produced mostly negative results (Blake et al., 2017; Harris and Mickes, 2014; Jones et al., 2018; Shirazi et al., 2020; Stern et al., 2020). If fluctuating hormones affect such wide-ranging behaviors, the effects must be small.

Stop & Check

11. At what time in a woman's menstrual cycle do her estradiol levels increase? When are they lowest?
12. When is a woman most likely to act sexy and initiate sexual activity?

See page 337 for the answer.

Parental Behavior

Hormonal changes during pregnancy prepare a female mammal to provide milk and also prepare her to care for the young. After she delivers the young, she increases her secretion of oxytocin and prolactin, which promote milk production and several aspects of maternal behavior (Rilling and Young, 2014). She eats and drinks more than usual, and she becomes less fearful and more aggressive in defense of the young. In male mammals that participate in care for the young, oxytocin is important for their parental behavior also (Inada et al., 2022).

In addition to secreting hormones, a female changes her pattern of hormone receptors. Late in pregnancy, sensitivity to estradiol increases in the brain areas important for maternal behavior and attention to the young (Rosenblatt et al., 1998), including the medial preoptic area and anterior hypothalamus and nucleus accumbens (Brown et al., 1996; Pereira and Ferreira, 2016). We have already encountered the preoptic area/anterior hypothalamus, or POA/AH, because of its importance for temperature regulation and thirst. Most brain areas participate in a variety of behavioral functions.

In humans, it has been demonstrated that pregnancy leads to decreased gray matter volume in several brain areas, as in Figure 10.10. (Hoekzema et al., 2017). Decreased brain volume sounds like a bad thing, but it is a result of pruning the most ineffective synapses. A similar process happens in adolescence, when brain volume also decreases. The brain areas that decrease volume during pregnancy are the areas that become most active when attending to the needs of a baby, and greater decreases in volume correlate with increased maternal attachment. In short, the brain change is an adaptive process.

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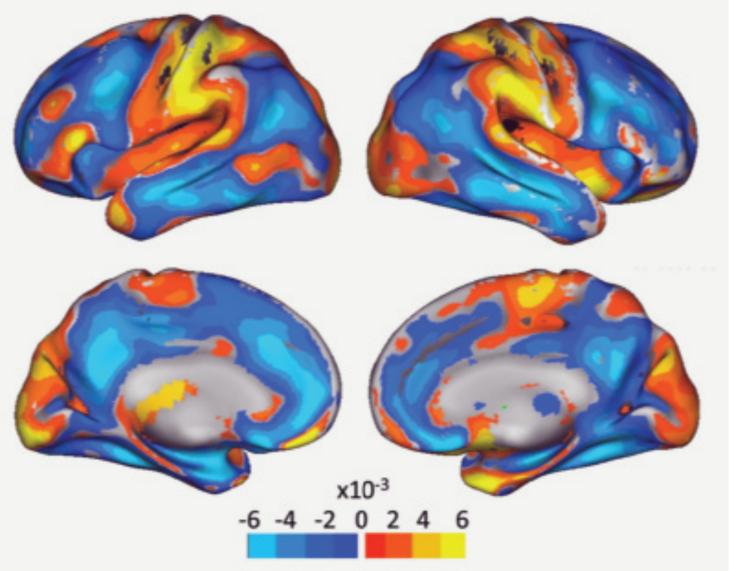
Figure 10.10 Areas that decrease volume during pregnancy

The decreased volumes correlate with increased responsiveness to infants. Evidently the brain prunes its least efficient synapses in these areas to increase responsiveness.

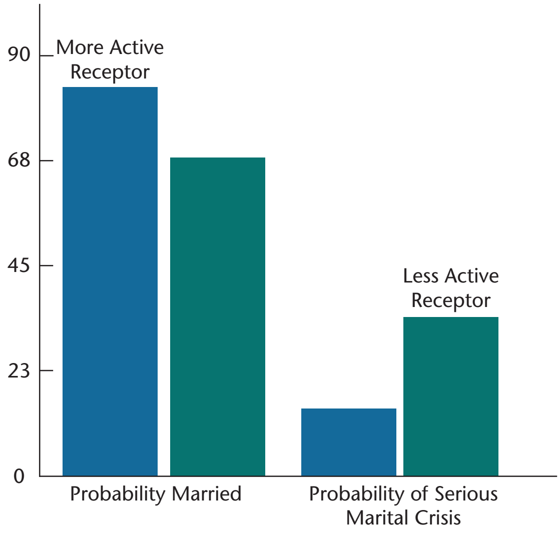


(**Source:** © Nature Neuroscience)

The hormone vasopressin is important for social behavior in many species. Male prairie voles, which secrete much vasopressin, establish long-term pair bonds with females and help rear their young. The males with the highest vasopressin levels show the highest level of sexual fidelity to their mates (Okhovat et al., 2015). Male meadow voles, which have low vasopressin levels, mate with a female and then ignore her and her young. Imagine a male meadow vole in a long, narrow cage. At one end, he can sit next to a female with which he has just mated. (She is confined there.) At the other end, he can sit next to a different female. Will he choose his recent mate (indicating loyalty) or the new female (seeking variety)? The answer: Neither. This little anti-social character sits right in the middle, as far away as possible from both of them. However, researchers found a way to increase activity of the genes responsible for vasopressin in the hypothalamus. Males with that treatment showed a strong attachment to a recent mate, and they even helped her take care of her babies (Lim et al., 2004). Whether the female was surprised, we don't know. In humans, researchers have reported that men with genes for less-active forms of the vasopressin receptor are less likely to marry, more likely to have marital conflicts or threat of divorce, and in general less likely to show altruistic behavior toward others (Walum et al., 2008; Wang et al., 2016; Figure 10.11). Women with the less-active form of the receptor were less attentive to their children (Avinun et al., 2012).

Figure 10.11 Effects of the vasopressin receptor in humans.

Men with the less active form of the receptor were less likely to marry, and more likely to have conflicts and possible divorce if they did marry.



(**Source:** Based on the results of Walum et al., 2008).

Ordinarily, female rats ignore or avoid baby rats, mainly because of an aversion to their odor. When a female gives birth, the delivery causes a change in her brain that makes the infants' odor more appealing (Lévy et al., 2004). However, suppose an experimenter leaves a female rat that has never been pregnant with some baby rats. Because the babies cannot survive without care, the experimenter periodically replaces them with new, healthy babies. Over a few days, the female gradually becomes more attentive, builds a nest, assembles the babies in the nest, licks them, and does everything else that normal mothers do, except nurse them. (Without giving birth, she does not secrete the prolactin and oxytocin necessary for milk production.) This experience-dependent behavior does not require hormonal changes and occurs even in females that had their ovaries removed (Mayer and Rosenblatt, 1979; Rosenblatt, 1967). It also occurs in male rats and mice, even though they ordinarily do not participate in care for the young (Horrell et al., 2021). In nature, male rats and mice would not remain close enough to the young to develop this effect. This process might seem like just a laboratory curiosity, but it is important in nature. Although hormonal changes trigger the early stage of maternal care, the mother's hormones start to decline a few days later. By that time, the experience of being with the young produces the same types of maternal behavior that the early hormones did (Rosenblatt, 1970; Stolzenberg and Champagne, 2016).

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In humans, the hormonal changes during pregnancy and delivery enable a mother to produce milk. Brain scans also indicate expansion of several areas in her brain from early to late pregnancy and then delivery, especially in areas responsible for reward and motivation. The amount of expansion in those areas correlates with the positive emotions a woman expresses about having a baby (Kim et al., 2016). In most respects, however, human parental behavior is experience-dependent rather than hormone-dependent.

Several studies have reported a correlation between fathers' hormones and their behavior toward their infants and toddlers. On average, a man's testosterone level declines and his prolactin level increases when a baby is born, but only if the man has a close relationship with the mother, and only in societies where men contribute to infant care (Edelstein et al., 2015; Storey and Ziegler, 2016). On average, men with lower testosterone levels and higher prolactin levels spend more time playing with and caring for their children (Gordon et al., 2010; Mascaro et al., 2013). Over the next few months after a baby is born, the father's testosterone level increases, and those with more rapid increases tend to contribute less to child care in some ways (Corpuz et al., 2021). Because all of these are correlational data, we do not know to what extent the hormones are the cause of the men's behavior, and to what extent they are the result.

Stop & Check

13. What factors are responsible for maternal behavior shortly after rats give birth? What factors become more important in later days?

See page 337 for the answer.

Module 10.1 | In Closing

Reproductive Behaviors and Motivations

Each of us is a product of our upbringing, and also a product of chemical influences that began before birth and continued thereafter. You can make a voluntary decision about how to handle your sexual motivations, but the motivations themselves have a biological basis.

Summary

1. Males and females evolve differences that make them more appealing to the other sex. This process is called sexual selection. **324**
2. Some of the behavioral differences between men and women can be interpreted in evolutionary terms, but the proposed explanations are more persuasive in some cases than in others. **325**
3. Genes on the X and Y chromosomes influence several aspects of sexual development by means other than hormones. **325**
4. Male and female behaviors differ because of sex hormones, but also because genes on the X and Y chromosomes exert direct effects on brain development. **325**
5. Organizing effects of a hormone during a sensitive period produce relatively permanent alterations in anatomy and physiology. **326**
6. In the absence of sex hormones, an infant mammal develops female-looking external genitals. Androgens shift development toward the male pattern. Estrogens, within normal limits, do not determine external anatomy. However, estrogens are essential for normal development of female internal anatomy. **328**
7. Many brain areas differ slightly on average between males and females, on average. The mechanisms behind the differences vary from one area to another. Any individual's brain area has a mosaic of male-typical, female-typical, and neutral aspects. **329**
8. On average, boys and girls tend to prefer different toys and different styles of play. Prenatal hormones influence those preferences. **331**
9. In adulthood, sex hormones activate sex desires by facilitating activity in parts of the hypothalamus. **331**
10. A woman's menstrual cycle depends on a feedback cycle that controls the release of hormones. Although women can respond sexually at any time in their cycle, sexual desire is greatest during the fertile period of the menstrual cycle, when estradiol levels are high. **332**
11. In mammals, hormones released around the time of giving birth facilitate maternal behavior. Prolonged exposure to young also induces parental behavior. **334**
12. Testosterone levels decline around the time of birth for many fathers, and those with lower testosterone levels tend to participate more in infant care. **336**

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Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

activating effects	**328**
androgens	**326**
estradiol	**327**
estrogens	**327**
follicle-stimulating hormone (FSH)	**332**
impotence	**332**
Klinefelter syndrome	**326**
luteinizing hormone (LH)	**332**
menstrual cycle	**332**
Müllerian ducts	**326**
organizing effects	**327**
ovaries	**326**
oxytocin	**331**
preovulatory period	**334**
progesterone	**327**
sensitive period	**327**
sexual selection	**324**
SRY gene	**326**
steroid hormones	**327**
testes	**326**
testosterone	**327**
Turner syndrome	**326**
Wolffian ducts	**326**

Thought Questions

1. The presence or absence of testosterone determines whether a mammal will differentiate as a male or a female. In birds, the story is the opposite: The presence or absence of estrogen is critical (Adkins and Adler, 1972). What problems would sex determination by estrogen create if that were the mechanism for mammals? Why do those problems not arise in birds? (Hint: Think about the difference between live birth and hatching from an egg.)
2. Many antipsychotic drugs, such as haloperidol and chlorpromazine, block activity at dopamine synapses. What side effects might they have on sexual behavior?

Stop & Check Answers

1. For a man to spread his genes, he should be certain that the children he supports are his own. If the woman to whom he is bonded mates with another man, she threatens that certainty.
2. The Turner syndrome and Klinefelter syndrome correlate with decreased fertility. The Klinefelter syndrome and the XYY conditions correlate with an increased probability of impaired learning or cognition.
3. The SRY gene causes the undifferentiated gonads of a mammal to develop into testes, which then produce testosterone and MIH to direct development toward the male pattern.
4. A mammal exposed to high levels of both male and female hormones will appear male.
5. A mammal exposed to low levels of both will appear female. External genital development depends on the presence or absence of androgens.
6. A female that lacked alpha-fetoprotein would be masculinized by her own estradiol, as researchers have in fact demonstrated (Bakker et al., 2006).
7. The mechanisms for sexual differentiation vary from one brain area to another. People vary in the genetics and epigenetics that modify brain development in different brain areas.
8. Girls whose mothers had higher testosterone levels during pregnancy tend to play with boys' toys more than the average for other girls.
9. Testosterone primes hypothalamic cells to be ready to release dopamine.
10. Many antidepressants increase serotonin, which inhibits dopamine release. Dopamine facilitates sexual activity.
11. Estradiol levels increase during the days leading up to the middle of the menstrual cycle. They are lowest during and just after menstruation.
12. During the periovulatory period.
13. The early stage of rats' maternal behavior depends on a surge in the release of prolactin and estradiol. A few days later, experience with the young maintains maternal behavior after the hormone levels begin to drop.

Module 10.1 | End-of-Module Quiz

1. What is meant by the term "sexual selection"?
   - **a.** Having an XX or XY chromosome pattern determines whether one develops as a female or a male.
   - **b.** Hormones during a sensitive period produce long-lasting effects on anatomy and behavior.
   - **c.** Some people choose to change their gender identity.
   - **d.** Evolution favors characteristics that make an individual more appealing to the opposite sex.

2. What does the *SRY* gene do?
   - **a.** It increases mammalian parental behavior.
   - **b.** It controls the production of prolactin.
   - **c.** It causes a mammalian embryo to develop into a female.
   - **d.** It causes a mammalian embryo to develop into a male.

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3. What is the chromosome pattern for a person with Turner syndrome?

a. YY
b. XXY
c. XYY
d. XO

4. Would it be possible to have both a pair of testes and a pair of ovaries? If not, why not?

a. Yes, it would be possible.
b. No, because testes and ovaries develop from the same primitive structure.
c. No, because the body would not have enough room for both types of structure.
d. No, because androgens and estrogens are chemically incompatible.

5. When do organizing effects of sex hormones occur in humans?

a. Equally at all times of life
b. During adulthood
c. Only during prenatal development
d. During prenatal development and at puberty

6. What would cause a genetic female to develop masculinized external anatomy?

a. An XO chromosome pattern
b. Insufficient estrogens during prenatal development
c. Prenatal exposure to extra androgens
d. Premature birth

7. What would cause a genetic male to develop feminized external anatomy?

a. An XYY chromosome pattern
b. Lack of androgen receptors
c. Prenatal exposure to extra estrogens
d. Premature birth

8. Why do most people have a mixture of male-typical and female-typical brain structures?

a. Early childhood experiences promote growth in different brain areas.
b. The X chromosome occurs in some cells and the Y chromosome occurs in others.
c. Different brain areas differentiate by different mechanisms and at different times.
d. Brain anatomy develops at random.

9. Prenatal sex hormones influence which of the following?

a. Probability of developing absolute pitch
b. Eye color
c. Political preferences
d. Childhood toy and play preferences

10. How do androgens and estrogens increase sexual motivation?

a. By priming the hypothalamus to release dopamine
b. By priming the hypothalamus to release serotonin
c. By increasing heart rate and blood pressure
d. By increasing attention to social signals

11. What does the combination pill for birth control contain?

a. Estradiol and testosterone
b. Testosterone and insulin
c. Estradiol and progesterone
d. Oxytocin and vasopressin

12. How does mammalian maternal behavior change over time after giving birth?

a. It becomes more dependent on the parasympathetic nervous system instead of the sympathetic.
b. It becomes more dependent on smell and less dependent on vision.
c. It becomes less dependent on hormones, more on experience with the young.
d. It becomes increasingly aggressive and less fearful.

Answers: 1d, 2d, 3d, 4b, 5d, 6c, 7b, 8c, 9d, 10a, 11c, 12c.

Module 10.2

Variations in Sexual Behavior

Learning Objectives

After studying this module, you should be able to:

7. Explain the relevance of intersex people for understanding the role of hormones in the development of sex-typed behaviors.
8. Discuss possible biological influences on the development of sexual orientation.

People vary in their gender identity and sexual orientation. In this module, we explore some of that diversity, including more common and less common conditions. You may or may not ever meet someone with one of the less common conditions (and you probably wouldn't know if you did), but the whole range of variation illustrates some important theoretical points about development.

Gender Identity and Gender-Differentiated Behaviors

For fish, sexual identity is more fluid than it is for humans. (Yeah, I know, terrible pun.) In the animated film *Finding Nemo*, after Nemo's mother died, in reality a clown fish father would change into a female at that point. However, the biologist who advised the film producers agreed that scientific accuracy on this point would have been more confusing to children than helpful (Cressey, 2016).

People are less flexible than fish, but we do vary in our sexual development. Let us specify from the start: "Different" does not mean "wrong." People differ naturally in their sexual development just as they do in anything else.

Gender identity is what we consider ourselves to be. The biological differences resulting from the chromosome pattern are *sex differences*, and the differences that result from people's regarding themselves as male or female are *gender differences.* To maintain this useful distinction, we should resist the trend to speak of the "gender" of fish, fruit flies, and so forth. Troops of monkeys or chimpanzees demonstrate different expectations for males and females, and in those cases it is reasonable to talk about gender, as well as gender nonconforming behavior (de Waal, 2022). But we should keep the useful distinction between sex differences (biology) and gender differences (psychological identification).

Most people accept the gender identity that matches their external appearance, but some do not. At one time, psychologists assumed that gender identity and related behaviors depended almost entirely how parents rear their children. However, several kinds of evidence suggest that prenatal hormones are important also.

Intersex People

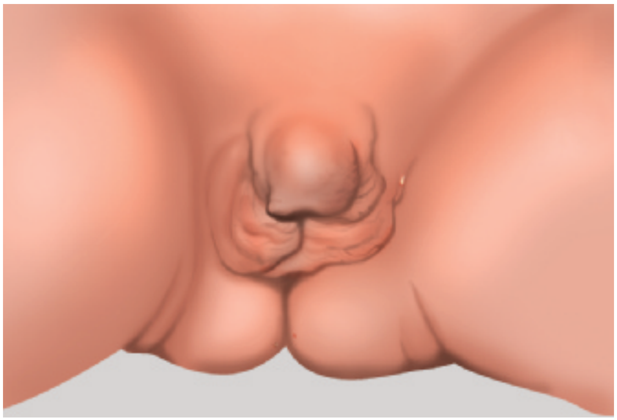
Recall that testosterone masculinizes the genitals and the hypothalamus during early development. A genetic male with low levels of testosterone or testosterone receptors may develop a female or intermediate appearance. A genetic female who is exposed to more testosterone than the average female can be partly masculinized.

The most common cause of an intermediate sexual anatomy is **congenital adrenal hyperplasia (CAH)**, meaning overdevelopment of the adrenal glands. Ordinarily, the adrenal glands have a negative feedback relationship with the pituitary gland. The pituitary secretes adrenocorticotropic hormone (ACTH), which stimulates the adrenal gland to release cortisol and other hormones, and cortisol feeds back to decrease ACTH. If a fetus has a genetic limitation in the ability to produce cortisol, the pituitary fails to receive the usual feedback signal, and it continues secreting more ACTH, stimulating the adrenal gland beyond the usual level. In addition to cortisol, the adrenal gland releases moderate amounts of testosterone and estradiol. The extra ACTH causes the adrenal gland to secrete extra testosterone, which has little effect on male development, but partly masculinizes the external genitals of a female. (The ovaries and other internal organs are less affected.) Figure 10.12 offers an example. After birth, the child receives medical treatments to bring the adrenal hormones within normal levels.

Someone with intermediate sexual development, as in Figure 10.12, is an **intersex person**. An alternative is to use the term *differences of sexual development.* It is estimated that at least 1 child in 100 in the United States is born with some degree of genital ambiguity, and at least 1 in 2,000 has enough ambiguity to make the male or female assignment uncertain (Blackless et al., 2000). The accuracy of these estimates is uncertain, as hospitals and families keep the information private. Confidentiality is important, but an unfortunate consequence is that intersex people have trouble finding others like themselves. For more information, consult the website of interACT: Advocates for Intersex Youth.

Figure 10.12 External genitals of a genetic female, age 3 months

The genitals were masculinized by excess androgens from the adrenal gland before birth.



(**Source:** Wellcome Image Library/Custom Medical Stock Photo.)

Stop & Check

14. What might partly masculinize the external appearance of a genetic female (XX)?

See page 347 for the answer.

Interests and Preferences of Girls with CAH

In most places, the policy has been to raise most intersex children as girls, on the assumption that surgery could make them look like more typical girls, and they would develop behaviors corresponding to the way they were reared. However, their brains were exposed to elevated testosterone levels during prenatal and early postnatal life. What happened to their behavior? As discussed in the first module of this chapter, prenatal levels of testosterone correlate with girls' toy choices. The same idea applies here. In several studies, girls with CAH were observed in a room full of toys—including some that were girl typical (dolls, plates and dishes, cosmetics kits), some that were boy typical (toy car, tool set, gun), and some that were neutral (puzzles, crayons, board games). The girls with CAH played with boys' toys more than most other girls did, but less than the average for boys (Pasterski et al., 2005, 2011). The girls exposed to the largest amount of testosterone in early development showed the largest preference for boys' toys (Berenbaum et al., 2000; Nordenström et al., 2002). You might wonder whether the parents, knowing that these girls had been partly masculinized in appearance, might have encouraged masculine-typical activities. Observations found that the parents generally encouraged the girls to play with whatever they wanted to play with (Wong et al., 2013). Compared to other girls, girls with CAH are less likely to imitate what women or young girls do (Hines et al., 2016). That is, the prenatal testosterone weakens their tendency to be socialized the way most other girls are. Another difference is that on average, girls with CAH also perform slightly better than most other girls on spatial and mechanical skills (Berenbaum et al., 2012; Hampson and Rovet, 2015).

When the girls who had CAH reach adolescence, their interests tend to be intermediate between those of typical males and females. Compared to other girls, they tend to read more sports magazines and fewer style and glamour magazines (Berenbaum, 1999). In adulthood, they are likely to express more physical aggression than most other women do, and less interest in infants (Mathews, Fane, Conway, Brook, and Hines, 2009). They tend to be more interested in rough sports and more likely than average to enter male-dominated occupations such as auto mechanic and truck driver (Frisén et al., 2009). About 90–95 percent identify as female (Berenbaum and Beltz, 2021; Meyer-Bahlburg et al., 2016). Although most identify as heterosexual, a higher than usual percentage are lesbian or bisexual (Daae et al., 2020).

Testicular Feminization

If someone with an XY chromosome pattern has a deficiency in the receptor for androgens, circulating androgens have little or no effect. This condition, known as **androgen insensitivity** or **testicular feminization**, produces an anatomy ranging from a smaller than average penis to an external appearance of a typical female, in which case no one has any reason to suspect the person is anything other than female, until puberty. Then, although the breasts develop and hips broaden, menstruation does not occur, because the body has undescended testes instead of ovaries and a uterus. The vagina is short and leads to nothing but skin. Also, pubic hair is sparse or absent, because it depends on androgens in females as well as males. Psychological development is that of a typical female (Figure 10.13).

Stop & Check

15. If a genetic female is exposed to extra testosterone during prenatal development, what behavioral effect is likely?
16. What would cause a genetic male (XY) to develop a partly feminized external anatomy?

See page 347 for the answer.

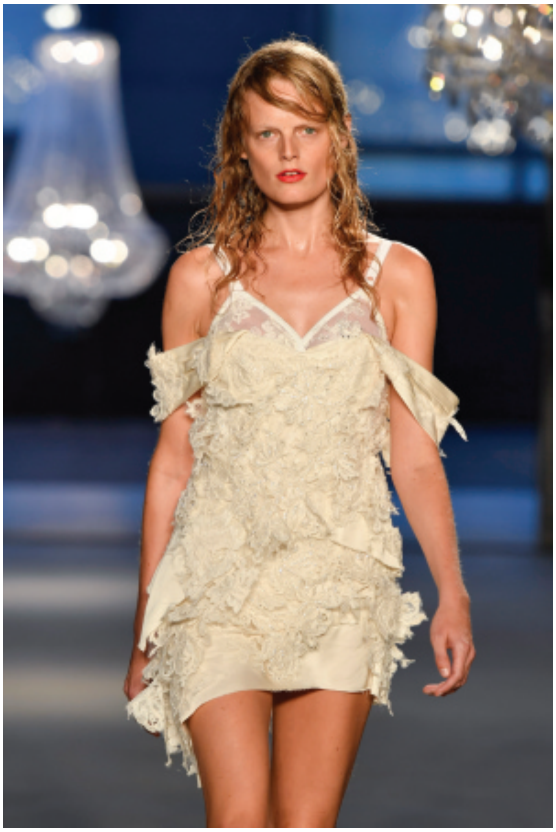
Discrepancies of Sexual Appearance

To resolve the roles of rearing and hormones in determining gender identity, the most decisive observation would come from rearing a normal male baby as a female or rearing a normal female baby as a male. If the resulting adult fully accepts the assigned role, we would know that upbringing determines gender identity. Although no one would perform such an experiment intentionally, we can learn from accidental events. In some cases, someone was exposed to a more-or-less normal pattern of male hormones in early development but then reared as a girl.

One type of case was reported first in the Dominican Republic in the 1970s, and then in other places, usually in

Figure 10.13 A fashion model who had testicular feminization

Hanne Odiele was born with undescended testes, producing testosterone that was without effect. She was always female in both appearance and behavior. She "came out" to encourage greater acceptance of intersex conditions.



Victor Virgile/Gamma-Rapho/Getty Images

communities with much inbreeding. Some genetic males fail to produce *5α-reductase 2*, an enzyme that converts testosterone to *dihydrotestosterone*, which is more effective than testosterone for masculinizing the external genitals. At birth, these individuals appear to be female, although some have a swollen clitoris and somewhat "lumpy" labia. Although they are considered girls and reared as such, their brains had been exposed to male levels of testosterone during early development. At puberty, the testosterone levels increase sharply, and even without conversion to dihydrotestosterone, the result is enough growth of a penis and scrotum to be clearly male.

Imagine that that you grew up as a girl, until at age 12 years, your external genitals suddenly changed from female to male. Would you say, "Okay, I'm a boy now"? Most of these people reacted exactly that way. The girl-turned-boy developed a male gender identity and directed his sexual interest toward females (Cohen-Kettenis, 2005; Imperato-McGinley et al., 1974). Remember, these were not typical girls. Their brains had been exposed to male levels of testosterone from prenatal life onward. Later results from 44 countries found that many but not all such people changed their identity from female to male during adolescence, with percentages that vary across countries (Batista and Mendonca, 2020).

A particularly disturbing case concerns one infant boy whose penis foreskin would not retract enough for easy urination. His parents took him to a physician to circumcise the foreskin, but the physician, using an electrical procedure, set the current too high and accidentally burned off the entire penis. On the advice of respected authorities, the parents elected to rear the child as a female, with surgery. What makes this case especially interesting is that the child had a twin brother (whom the parents did not let the physician try to circumcise). If both twins developed gender identities matching their assigned sexes, one as a girl and the other as a boy, the results would indicate that rearing was decisive in gender identity.

Initial reports claimed that the child reared as a girl had a female gender identity, though she also had strong masculine tendencies (Money and Schwartz, 1978). By about age 10, she had figured out that something was wrong and that "she" was really a boy. She had preferred boys' activities and played only with boys' toys. She even tried urinating in a standing position, despite always making a mess. By age 14, she insisted that she wanted to live as a boy. At that time, her (now his) father tearfully explained the earlier events. The child changed names and identified as a boy. At age 25, he married and adopted his wife's children. Clearly, a biological predisposition had won out over the family's attempts to rear the child as a girl (Colapinto, 1997; Diamond and Sigmundson, 1997). A few years later, the story ended tragically with this man's suicide.

We should not draw universal conclusions from a single case. However, the point is that it was a mistake to impose surgery and hormonal treatments to try to force this child to become female. When the prenatal hormone pattern of the brain conflicts with a child's appearance, no one can be sure how that child will develop psychologically. Hormones don't have complete control, but rearing patterns don't, either.

Stop & Check

17. What caused some people's genitals to appear female at birth, but develop the male pattern at adolescence?

See page 347 for the answer.

Issues of Gender Assignment and Rearing

Girls with CAH and related conditions are born with appearances ranging from almost typical female to a partly masculinized external appearance. Some genetic males are born with a very small penis because of a condition called *cloacal exstrophy*, a defect of pelvis development (Reiner and Gearhart, 2004). Despite their genital anatomy, they had typical male levels of testosterone in prenatal development.

How should children with either of these conditions be reared? Beginning in the 1950s, medical doctors recommended that anyone with intermediate or ambiguous

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genitals should be reared as a girl, using surgery if necessary to make the genitals look more feminine (Dreger, 1998). The reason was that surgery to approximate female appearance is easier than surgery to approximate male appearance. Physicians and psychologists assumed that if a child looks like a girl and the parents rear her as a girl, she will fully accept that identity.

And she lives happily ever after, right? Not necessarily. Of the males with cloacal exstrophy who are reared as girls, nearly all develop typical male interests, nearly all develop sexual attraction toward women, and many or most eventually demand reassignment as males (Reiner and Gearhart, 2004). That result demonstrates a strong effect of prenatal hormones on sexual orientation.

Girls with the CAH history have a difficult sexual adjustment, especially if they were subjected to clitoris-reduction surgery to make them look more female. A surgically created or lengthened vagina provides no sensation and requires frequent attention to prevent it from scarring over. Many women subjected to such surgery have urinary incontinence and significant sexual difficulties, including lack of orgasm. Many report little sexual pleasure. In one study, 25 percent said they had never had a love relationship of any type (Jürgensen et al., 2013). Many intersex people wish they had their original enlarged clitoris instead of the mutilated, insensitive structure left to them by a surgeon. Moreover, they resent being deceived. Historian Alice Dreger (1998) describes one intersex person:

> As a young person, [she] was told she had "twisted ovaries" that had to be removed; in fact, her testes were removed. At the age of twenty, "alone and scared in the stacks of a [medical] library," she discovered the truth of her condition. Then "the pieces finally fit together. But what fell apart was my relationship with both my family and physicians. It was not learning about chromosomes or testes that caused enduring trauma, it was discovering that I had been told lies. I avoided all medical care for the next 18 years. . . . [The] greatest source of anxiety is not our gonads or karyotype. It is shame and fear resulting from an environment in which our condition is so unacceptable that caretakers lie." (p. 192)

How should such a child be reared? Most are reared as girls, and most are reasonably satisfied with this designation, although some consider themselves gender-fluid and many are either lesbian or bisexual. Rearing a CAH genetic female as male has disadvantages, including the need to surgically remove the ovaries before puberty to prevent breast growth and other female-typical developments (de Jesus et al., 2019). Physicians have no clear consensus on whether surgery to "correct" the genital appearance should occur early, late, or not at all. They do agree that it should be an informed decision by the family (Speiser et al., 2018). The argument for surgery is that it improves the child's acceptance by others. The argument against it is that clitoris-reduction surgery decreases sexual pleasure.

Sexual Orientation

Contrary to what biologists and others once assumed, same-sex genital contact occurs in nature for many animal species, and not just in those that cannot find a member of the opposite sex, or those with hormonal abnormalities (Bagemihl, 1999). Exclusive, lifelong same-sex orientation has so far been observed only in humans and sheep, although it may occur in others (Bailey et al., 2016). Frans de Waal (2022), who spent his career observing primates, described all bonobos as "bisexual." If "natural" means "occurs in nature," then same-sex activity is natural.

People *discover* their sexual orientation. They choose their actions, but they do not choose their desires or orientation, any more than people choose to be left-handed or right-handed. Whereas most men discover their sexual orientation early, many women are slower. Boys' feminine-type behaviors in childhood and adolescence correlate strongly with same-sex orientation in adulthood (Cardoso, 2009; Alanko et al., 2010), but girls' masculine-type behaviors are relatively weak predictors of sexual orientation (Alanko et al., 2010; Udry and Chantala, 2006).

Surveys report that about 3.5 percent of adults in the United States identify as gay or lesbian (Gates, 2011). The percentage varies depending on how the question is worded (Bailey et al., 2016). To a question like, "Have you ever had any same-sex contact or same-sex attraction," the percentage goes up (Norris et al., 2015). The percentage also varies among countries, although we do not know how much of the apparent difference is due to secrecy or inaccurate reporting.

Bisexuality and sexual fluidity are more common in women than in men (Diamond, 2007; Ward et al., 2014; Xu et al., 2021). Fewer men are fully bisexual, although many identify as "mostly straight" or "mostly gay" (Savin-Willliams, 2016). Even though a man may have had both same-sex and opposite-sex experiences, his preference and fantasies almost always lean strongly one way more than the other, and few men change their orientation (Norris et al., 2015; Rieger et al., 2005).

Behavioral and Anatomical Differences

Gay men and heterosexual men differ slightly on average in height, weight, shape of the face, sound of the voice, and ratio of the index finger to the ring finger (Bogaert, 2010; Skorska et al., 2015; Suire et al., 2020; Tasos, 2021). However, let's emphasize the terms "slightly" and "on average." The difference in height is on average only half an inch (1.5 cm).

People who differ in sexual orientation also tend to differ in many behaviors not directly connected to sex. Gay men are more likely than average to choose female-typical careers such as florist or hair stylist (Semenyna and Vasey, 2016). Also, whereas heterosexual men usually give directions in terms of distances and north, south, east, or west, women and gay men are more likely to describe landmarks (Hassan and Rahman, 2007). Again, remember that these are differences "on average."

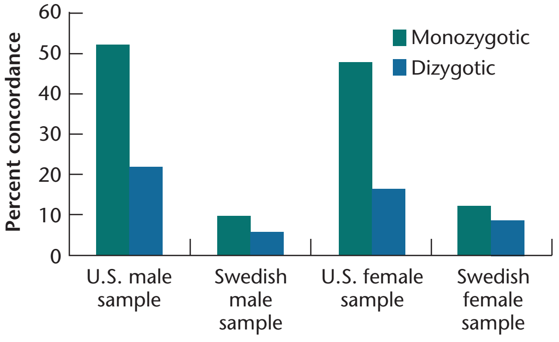
Genetics

Early studies of the genetics of human sexual orientation began by advertising in gay or lesbian publications for readers of those magazines who had twins. When someone responded, the researchers contacted the other twin to fill out a survey with miscellaneous questions that included sexual orientation. The results showed a stronger concordance (agreement) for monozygotic than dizygotic twins (Bailey et al., 2016). Note, this does *not* say that monozygotic twins are more likely to have a same-sex orientation than dizygotic twins are. It says that monozygotic twins are more likely to have the *same* sexual orientation.

However, the kind of person who answers an ad in a gay or lesbian magazine is not representative of all others. A later study examined the data from all the twins in Sweden between ages 20 and 47 (Långström et al., 2010). The Swedish study differed not only in the breadth of the sample but also in the behavioral criterion. Instead of asking about sexual orientation, the researchers asked whether someone had ever had a same-sex partner. Figure 10.14 compares the data from the two studies. The results do not indicate number of people with same-sex activity or orientation. Rather, they indicate concordance—the probability of same-sex activity or orientation in one twin, given that the other twin had already indicated such activity. Although both sets of results show a higher concordance for monozygotic than dizygotic twins, note the huge difference in results. Other studies of twins in several countries also found higher concordance for sexual orientation in monozygotic than dizygotic twins, but the magnitude of the effect has varied considerably (Alanko et al., 2010; Burri et al., 2011). Modern methods enable researchers to compare chromosomes. The results have identified a few sites where one form of a gene is somewhat more common in gay men than heterosexual men, but no common gene has more than a small effect (Sanders et al., 2017). In short, the results indicate some heritability of sexual orientation, but the size of the effect is uncertain, and the mechanism is also uncertain.

Figure 10.14 Twin concordance for same-sex orientation or activity

The concordance for same-sex orientation (U.S. study) or activity (Swedish study) was higher for monozygotic twins than for dizygotic twins.



(**Source:** Based on the data of Bailey and Pillard, 1991; Bailey et al., 1993; Långström et al., 2010).

An Evolutionary Question

On average, a gay man has about one-fifth as many children as a heterosexual man. If a homosexual orientation has a genetic basis, why hasn't evolution selected strongly against those genes? Several hypotheses are worth considering. One is that genes for same-sex orientation are maintained by kin selection. That is, those who do not have children themselves might do a better than average job of helping their siblings rear children. Survey data in the United States indicate that gay men are no more likely, and perhaps less likely, than heterosexuals to support their relatives (Bobrow and Bailey, 2001). However, observations in Samoa found that gay men are more helpful than average toward their nephews and nieces, in ways such as baby-sitting, tutoring, or contributing money (Vasey and VanderLaan, 2010). It is difficult to know what might have been the usual pattern through human existence.

A second idea is that sexual orientation relates to epigenetics rather than changes in DNA sequence (Rice et al., 2012). It is possible for environmental events to attach an acetyl group or a methyl group (CH_3) to activate or inactivate a gene. Some epigenetic changes persist from one generation to the next. Perhaps epigenetic changes affect certain genes often enough to produce the observed variation in sexual orientation.

According to a third hypothesis, genes that produce same-sex orientation might produce advantages for their relatives, increasing their probability of reproducing. Studies in several countries have reported that relatives of gay men have a somewhat greater than average number of children (Camperio-Ciani et al., 2004; Schwartz et al., 2010; Semenyna et al., 2017).

A variant of this hypothesis is that certain genes might lead to same-sex orientation in some people and other outcomes in their relatives. Researchers identified genes that were more common than average among people who had at least one same-sex encounter. They then found that heterosexual people with those same genes tended to have numerous sexual partners (Zietsch et al., 2021). A major limitation of this study is that having an occasional same-sex experience is not the same as being gay or lesbian. The genes that the researchers found may reflect openness to new experiences, or willingness to take risks, or just a strong sex drive, rather than same-sex attraction (Reardon, 2021).

Stop & Check

18. For which kind of twin pair is the concordance for sexual orientation greatest?
19. It seems difficult to explain how same-sex orientation could remain moderately common if most gay men do not reproduce. How would the hypothesis about epigenetics help with the explanation?

See page 347 for the answer.

Prenatal Influences

Adult hormone levels do *not* explain sexual orientation. On average, gay and heterosexual men have nearly the same hormone levels, and most lesbian women have about the same hormone levels as heterosexual women. However, it is possible that sexual orientation depends on hormone levels during a sensitive period of brain development (Ellis and Ames, 1987; Reinisch et al., 2017). Animal studies have shown that prenatal or early postnatal hormones produce organizing effects on both external anatomy and brain development, but the external anatomy develops earlier than the brain. Therefore, it is possible for hormones to alter the brain without changing external anatomy. Still, this is a speculative hypothesis.

The mother's immune system offers another possibility. Studies in several countries report that a gay orientation is slightly more probable among men who have older brothers, regardless of the number of sisters and younger brothers (Blanchard, 2008; Bogaert, 2003b; Bozkurt et al., 2015; Purcell et al., 2000; Schwartz et al., 2010). Furthermore, what matters is having *biological* older brothers. Growing up with older stepbrothers or adopted brothers has no apparent influence. Having a biological older brother has an influence, even if the brothers were reared separately (Bogaert, 2006). The influence does not stem from social experiences, but rather from how many previous times the mother gave birth to a son. The probable explanation is that a mother's immune system occasionally reacts against a protein in a son and then attacks subsequent sons enough to alter their development. Researchers tested mothers of gay sons with older brothers and found elevated levels of antibodies against a protein produced by the Y chromosome (Bogaert et al., 2018). This explanation fits with the observation that later-born gay men tend to be shorter than average (Bogaert, 2003a).

Another hypothesis relates to stress on the mother during pregnancy. Research has shown that prenatal stress alters sexual development in laboratory animals. In several experiments, rats in the final week of pregnancy had the stressful experience of confinement in tight Plexiglas tubes for more than 2 hours each day under bright lights. In some cases, they were given alcohol as well. Their daughters looked and acted approximately normal. The sons, however, despite normal male anatomy, often responded to the presence of another male by arching their backs in the typical rat female posture for sex (I. L. Ward et al., 1994). Males that were subjected to both stress and alcohol in prenatal development had decreased male sexual behaviors as well as the increased female behaviors (I. L. Ward et al., 1999).

Prenatal stress and alcohol may alter brain development through several routes. Stress releases endorphins, which can antagonize the effects of testosterone on the hypothalamus (O. B. Ward et al., 1986). Stress also elevates levels of certain adrenal hormones (corticosterone in rats, cortisol in human) that decrease testosterone release (O. B. Ward et al., 2002; M. T. Williams et al., 1999). The long-term effects of either prenatal stress or alcohol include several changes in the structure of the nervous system (Nosenko and Reznikov, 2001; I. L. Ward et al., 1999).

Although these studies pertained to rats, they prompted investigators to examine possible effects of prenatal stress on humans. Three surveys asked mothers of sons whether they experienced any unusual stress during pregnancy. In two of the three, the mothers of sons with a same-sex orientation recalled more than average stressful experiences (Bailey et al., 1991; Ellis et al., 1988; Ellis and Cole-Harding, 2001). However, these studies relied on women's memories of pregnancies more than 20 years earlier. A better but more difficult procedure would be to measure stress during pregnancy and examine the sons' sexual orientation many years later.

In short, researchers have identified several possible biological influences on sexual orientation, but much remains unknown. The research on males has been more extensive than that on females.

Stop & Check

20. How might having an older brother increase the probability of a gay orientation?
21. How might stress to a pregnant rat alter the sexual orientation of her male offspring?

See page 347 for the answer.

Brain Anatomy

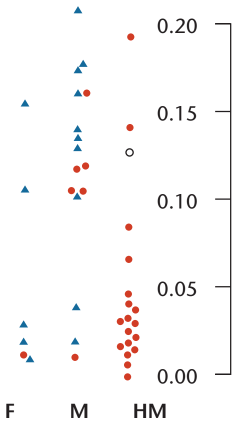
Do brains also differ as a function of sexual orientation? The results are complex. On average, the brains of gay men resemble those of heterosexual men in most ways, but they are shifted partly in the female-typical direction for a few structures. Similarly, the brains of lesbians resemble those of heterosexual women in most ways, but they are shifted in the male direction in a few ways (Frigerio et al., 2021; Rahman and Wilson, 2003).

The most widely cited research concerns the third interstitial nucleus of the anterior hypothalamus (INAH-3), which is generally more than twice as large in heterosexual men as in women. This area has more cells with androgen receptors in men than in women (Shah et al., 2004), and it probably plays a role in male sexual behavior, although the exact role is uncertain. In other species it is known as the *sexually dimorphic nucleus*, although calling it a "nucleus" is a bit of an overstatement. It is a subdivision of a subdivision of the preoptic hypothalamus.

Simon LeVay (1991) examined INAH-3 in 41 people who had died between the ages of 26 and 59. Of these, 16 were heterosexual men, 6 were heterosexual women, and 19 were gay men. All of the homosexual men, 6 of the 16 heterosexual men, and 1 of the 6 women had died of AIDS. LeVay found that the mean volume of INAH-3 was larger in heterosexual men than in heterosexual women or gay

Figure 10.15 Volumes of the interstitial nucleus 3 of the anterior hypothalamus (INAH-3)

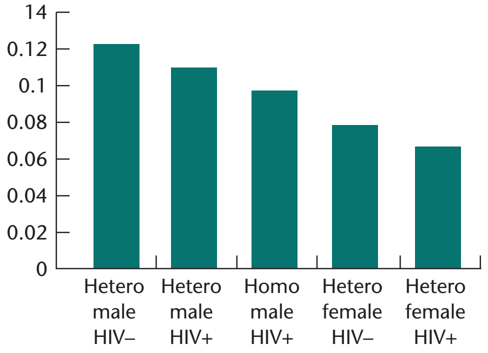
Samples are females (F), heterosexual males (M), and gay males (HM). Each filled circle represents a person who died of AIDS, and each triangle represents a person who died from other causes. The one open circle represents a bisexual man who died of AIDS.



(**Source:** Reprinted with permission from "A difference in hypothalamic structure between heterosexual and homosexual men," by S. LeVay, *Science, 253*, pp. 1034–1037. Copyright © 1991 American Association for the Advancement of Science.)

Figure 10.16 Another comparison of INAH-3

In this study, the mean volume for gay men was larger than that of heterosexual women but smaller than that of heterosexual men.



(**Source:** Based on data of Byne et al., 2001)

men, who were about equal in this regard. Figure 10.15 shows the distribution of volumes for the three groups. LeVay (1993) later examined the hypothalamus of a gay man who died of lung cancer; he had a small INAH-3, like the homosexual men who died of AIDS. In Figure 10.15, note the variation among individuals. If you could examine a man's INAH-3, you could make a reasonable guess about sexual orientation, but you could not be confident.

A later study partly replicated these trends. Researchers found that the INAH-3 nucleus of homosexual men was intermediate between those of heterosexual men and heterosexual women. Also, the volume was smaller in HIV-positive than HIV-negative individuals (Byne et al., 2001). Figure 10.16 displays the means for five groups. On microscopic examination of the INAH-3, researchers found that heterosexual men had larger neurons than homosexual men but about the same number. Neither this study nor LeVay's earlier study included lesbians. Still another study found INAH-3 to be larger in heterosexual males than in transgender females (Garcia-Falgueras and Swaab, 2008).

To interpret these results, we need to ask whether differences in the hypothalamus influence sexual orientation, or sexual activity influences the size of hypothalamic neurons. Some neurons do grow or shrink in adults because of hormones or behavioral activities (Cooke et al., 1999). A nonhuman study offers suggestive results. About 8 percent of rams (male sheep) direct their sexual behavior toward other males. One area of the anterior hypothalamus is larger in female-oriented rams than in male-oriented rams and larger in male-oriented rams than in females (Roselli et al., 2004). (Whether this area corresponds to human INAH-3 is uncertain.) This area becomes larger in male than female sheep before birth as a result of prenatal testosterone levels (Roselli et al., 2007). In sheep, at least, an anatomical difference appears before any sexual behavior, and so it is more likely a cause than a result. The same may or may not be true in humans.

Stop & Check

22. In LeVay's study, what evidence suggests that INAH-3 volume relates to sexual orientation rather than AIDS?

See page 347 for the answer.

Transgender People

Transgender people are those who affirm that they were "born in the wrong body," that although their anatomy appears male or female, they clearly identify with the other gender. Estimates of the prevalence of transgender people in the United States range from 0.3 to 0.6 percent, but these may be underestimates, because many transgender people prefer to avoid public identification. The prevalence of transgender people has increased since about 2005, especially female-to-male transitions (Graham, 2022). Transgender people have some interests and activities that are not typical of their birth sex, but most people with gender-atypical interests or activities do not identify as transgender (Berenbaum, 2018).

Some aspects of brain anatomy of transgender people resemble others of their birth sex, some aspects resemble those of their experienced gender, and some are intermediate (Frigerio et al., 2021; Kurth et al., 2022; Mueller et al., 2021). These data are averages, and every individual is different. Two areas that are most likely to match the

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experienced gender are the INAH-3 nucleus, which correlates with sexual orientation, and one extension of the amygdala that pertains to sexual behavior but not to sexual orientation (Garcia-Falgueras and Swaab, 2008; Zhou et al., 1995). Being transgender does not correlate perfectly with sexual orientation. The honest answer is that the basis for being transgender is not understood.

When someone reaches adolescence and requests a gender change, the recommendation is as follows (Graham, 2022): It is unwise to make irreversible physical changes at once, because many children who say they want to be the opposite sex change their mind during the teenage years (Hayward, 2022). Puberty-blocking drugs (to prevent body changes corresponding to the original, rejected sex) can be given to children at least 12 years old who have intense distress about their assigned gender. It is important to get informed consent, which can be tricky for 12-year-olds, and some have regretted their decision later. At age 16, if the adolescent still wishes to proceed, treatment can start with hormones of the desired sex. Surgery, if desired, can be done at age 18 or later. In most cases, people who have both requested and received this set of treatments have reported improvement in their mental health (D'hoore and T-Sjoen, 2022).

Module 10.2 | In Closing

We Are Not All the Same

When Alfred Kinsey conducted the first massive surveys of human sexual behavior in the middle of the 20th century, he found that most of the people he interviewed considered whatever their own behavior was to be "normal." Many believed that sexual activity more frequent than their own was abnormal and might even lead to insanity (Kinsey et al., 1948; Kinsey et al., 1953).

How far have we come since then? People today are more aware and generally more accepting of sexual diversity than they were in Kinsey's time. Still, intolerance remains common. Biological research will not tell us how to treat one another, but it can help us understand how we come to be different.

Summary

1. People can develop ambiguous genitals or genitals that don't match their chromosomal sex for several reasons. The most common is congenital adrenal hyperplasia, in which a genetic defect in cortisol production leads to overstimulation of the adrenal gland and therefore extra testosterone production. When that condition occurs in a female fetus, she becomes partly masculinized. Those with intermediate genitals are called intersex people. **339**
2. On average, girls with a history of congenital adrenal hyperplasia show more interest in boy-typical activities than other girls do. **340**
3. Testicular feminization, or androgen insensitivity, is a condition in which someone with an XY chromosome pattern is partly or fully insensitive to androgens and therefore develops a female appearance. **340**
4. Some children have a gene that decreases their early production of dihydrotestosterone. Such a child looks female at birth and is considered a girl but develops a penis at adolescence. Many of them then adopt a male gender identity. **341**
5. Physicians sometimes recommend surgery to make intersex people look more feminine. However, clitoris-reduction surgery decreases sexual pleasure. No consensus has yet arisen about the proper decision. **341**
6. Physical differences associated with sexual orientation are small and variable. **342**
7. Biological explanations for variations in sexual orientation include genetics, prenatal hormones, and (in males) reactions by the mother's immune system. Adult hormone levels do not significantly correlate with sexual orientation. **342**
8. Several hypotheses attempt to explain the prevalence of same-sex orientation in the population despite the fact that it correlates with having fewer children. **343**
9. On average, one part of the hypothalamus is larger in heterosexual men than in gay men. **344**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

androgen insensitivity	**340**
congenital adrenal hyperplasia	**339**
gender identity	**339**

intersex person **339**
testicular feminization **340**
transgender **345**

Thought Questions

1. On average, intersexes have IQ scores in the 110 to 125 range, well above the mean for the population (Dalton 1968; Ehrhardt and Money, 1967; Lewis et al., 1968). One possible interpretation is that a hormonal pattern intermediate between male and female promotes great intellectual development. Another possibility is that intersexuality may be more common in intelligent families than in less intelligent ones or that the more educated families are more likely to bring their intersex children to an investigator's attention. What kind of study would be best for deciding among these hypotheses? (For one answer, see Money and Lewis, 1966.)
2. Recall LeVay's study of brain anatomy in heterosexual and homosexual men. Certain critics have suggested that one or more of the men classified as "heterosexual" might have been gay or bisexual. If so, would that fact strengthen or weaken the overall conclusions?

Stop & Check Answers

14. A deficiency in the ability to produce cortisol decreases the negative feedback to the pituitary gland, which continues stimulating the adrenal gland. The adrenal gland then produces large amounts of its hormones, including testosterone, which masculinizes development.

15. A girl who is exposed to extra testosterone during prenatal development is more likely than most other girls to prefer boy-typical activities.

16. A genetic male with a gene that prevents testosterone from binding to its receptors will develop an appearance that partly or completely resembles a female.

17. Genetic males had a mutation that prevented conversion of testosterone to dihydrotestosterone, which is more effective at masculinizing the genitals. At puberty, the massive increase in testosterone produced masculinized appearance.

18. Monozygotic twins have higher concordance (similarity) than dizygotic twins.

19. According to this hypothesis, an event in the environment can attach an acetyl group or a methyl group to a gene, increasing or decreasing its activity. That type of epigenetic effect could occur often enough to maintain a certain prevalence of same-sex orientation.

20. Some mothers after giving birth to one or more sons develop antibodies against a protein that the Y chromosome makes. Those antibodies can alter brain development for a later son.

21. Stress can increase the release of endorphins in the hypothalamus, and high endorphin levels can block the effects of testosterone.

22. In his study, the average size of INAH-3 was about the same for heterosexual men who died of AIDS and those who died of other causes. One gayman who died of other causes had about the same size INAH-3 as gay men who died of AIDS.

Module 10.2 | End-of-Module Quiz

1. Congenital adrenal hypertrophy results from disrupted feedback between which two structures?
- **a.** The ovaries and the adrenal glands
- **b.** The adrenal glands and the pituitary
- **c.** The pituitary and the ovaries
- **d.** The hypothalamus and the pituitary

2. If a girl is exposed to more than average testosterone during prenatal development, the probable results include a significant effect on which of the following?
- **a.** Her intelligence
- **b.** Her toy preferences
- **c.** Her hair and eye colors
- **d.** Her visual acuity

3. Testicular feminization results in what outcome?
- **a.** An XY chromosome pattern with exaggerated male appearance
- **b.** An XX chromosome pattern with exaggerated female appearance
- **c.** An XY chromosome pattern with partly or entirely female appearance
- **d.** An XX chromosome pattern with partly or entirely male appearance

4. Studies on genetic males who fail to produce 5α-reductase 2 support what conclusion?
- **a.** Early rearing experiences determine gender identity and sexual orientation.
- **b.** Prenatal hormones influence gender identity and sexual orientation.
- **c.** Having an older brother influences sexual orientation.
- **d.** Most people's sexual orientation is fluid.

5. The conclusion that sexual orientation is partly heritable depends mainly on what evidence?
- **a.** Identification of a gene strongly linked to sexual orientation
- **b.** Comparisons of sexual orientation in many cultures
- **c.** Comparisons between monozygotic and dizygotic twins
- **d.** Comparisons between gay men and lesbian women

6. Which of the following increases the probability of a gay orientation?

- **a.** Living in a family with one or more older sisters
- **b.** Living in a family with an older, adopted brother
- **c.** Having a biological older brother, even if he did not live in the same house
- **d.** Having either an adopted or biological younger brother

7. In what way was INAH-3 distinctive for most of the gay men, in comparison to heterosexual men, in LeVay's study and the follow-up research?

- **a.** This nucleus had fewer than average neurons but only in men who died of AIDS.
- **b.** This nucleus had fewer than average neurons regardless of the cause of death.
- **c.** This nucleus had neurons with smaller than average volume.
- **d.** This nucleus had fewer neurons, but each of them had a larger than average volume.

Answers: 1d, 1b, 2b, 3c, 4b, 5c, 6c, 7c.

Suggestions for Further Reading

Bailey, J. M., Vasey, P. L., Diamond, L. M., Breedlove, S. M., Vilain, E., and Epprecht, M. (2016). Sexual orientation, controversy, and science. *Psychological Science in the Public Interest*, *17*, 45–101. An article that thoroughly and objectively reviews research on sexual orientation.

Colapinto, J. (2000). *As nature made him: The boy who was raised as a girl.* (HarperCollins). Describes the boy whose penis was accidentally removed, as presented on page **341**.

de Waal, F. (2022). *Different: Gender through the eyes of a primatologist.* (Norton). Discusses what studies of chimpanzees and other primates can and cannot tell us about sexual behavior, sexual orientation, and gender identity.

Pfaff, D. (2017). *How the vertebrate brain regulates behavior: Direct from the lab.* (Harvard University Press). Description of Pfaff's lifetime of research on the mechanisms of sexual behavior in female rats, which he enabled us to understand in much detail.

Chapter 11

People express emotion by facial expressions, gestures, and postures.
(Hibatallah Khawaja/EyeEm/Getty Images)

Emotional Behaviors

Chapter Outline

Module 11.1

What Is Emotion?

Emotion and Autonomic Arousal
Basic Emotions or Continuous Dimensions
The Functions of Emotion
In Closing: Emotions and the Nervous System

Module 11.2

Attack and Escape Behaviors

Attack Behaviors
Fear and Anxiety
Anxiety Disorders
Relief from Anxiety
In Closing: Doing Something about Emotions

Module 11.3

Emotional Reactions to Stress

Stress and the General Adaptation Syndrome
Stress and the Hypothalamus-Pituitary-Adrenal Cortex Axis
Coping with Stress
In Closing: Emotions and Body Reactions

Learning Objectives

After studying this chapter, you should be able to:

1. Discuss the role of the autonomic nervous system in emotional feelings.
2. Explain why many psychologists describe emotion in terms of continuous dimensions.
3. Discuss the role of emotions in moral reasoning.
4. Describe what is known about the genetics of aggression.
5. Evaluate the roles of testosterone, serotonin, and cortisol in aggressive behavior.
6. Discuss the role of the amygdala in emotional processing.
7. Describe biological aspects of anxiety disorders.
8. Comment on methods of relieving anxiety.
9. Define the general adaptation syndrome.
10. Describe the effects of stress on the nervous system and the immune system.
11. Discuss coping with stress.

Unfortunately, one of the most significant things ever said about emotion may be that everyone knows what it is until they are asked to define it.

Joseph LeDoux (1996, p. 23)

Suppose researchers have discovered a new species—let's call it species X—and psychologists begin testing its abilities. They place food behind a green card and nothing behind a red card and find that after a few trials, X always goes to the green card. We conclude that X demonstrates learning, memory, and hunger. Then researchers offer X a green card and a variety of gray cards; X still goes to the green, so it must have color vision and not just brightness discrimination. Next, they let X touch a blue triangle that is extremely hot. X makes a loud sound and backs away. Someone picks up the blue triangle (with padded gloves) and starts moving with it rapidly toward X. As soon as X sees this happening, it makes the same sound, turns, and starts moving rapidly away. Shall we conclude that it feels fear?

If you said yes, now let me add: I said this was a new species, and so it is, but it's a new species of robot, not animal. Do you still think X feels fear? Robots can have artificial intelligence, but we would be most reluctant to assume they feel emotion.

What would be convincing evidence that an animal feels emotion? When a dog runs away from a threat, you probably infer that it is afraid, but what about an insect that escapes as you approach? Was it afraid? If you disturb a beehive and the bees attack you, are they angry? How could you know? Emotion is a difficult topic because it implies conscious feelings that we cannot observe. Biological researchers refers mostly to emotional *behaviors,* which are observable, even if emotional feelings are not. Still, most of us hope eventually to understand the emotional experiences themselves.

Module 11.1

What Is Emotion?

Learning Objectives

After studying this module, you should be able to:

1. Discuss the role of the autonomic nervous system in emotional feelings.
2. Explain why many psychologists describe emotion in terms of continuous dimensions.
3. Discuss the role of emotions in moral reasoning.

By one definition, emotion includes "cognitive evaluations, subjective changes, autonomic and neural arousal, and impulses to action" (Plutchik, 1982, p. 551). That sounds okay, but by that definition, don't hunger and thirst count as emotions? One definition of motivation is "an internal process that modifies the way an organism responds to a certain class of external stimuli" (Numan and Woodside, 2010). By that definition, don't happiness, sadness, fear, and anger count as motivations? Distinguishing between motivation and emotion is difficult, and maybe there is no real difference. Lisa Feldman Barrett (2012) compared the "emotion" to "weeds": It is a category we might find useful, but it is not a distinction that nature makes.

A further problem with the usual definition is that cognition, feeling, autonomic arousal, and action do not always stick together. Sometimes you suddenly feel nervous (a feeling) and your heart is racing (autonomic arousal), but you don't know why (no cognition), and you do nothing about it (no action). At another time you could think "COVID is dangerous" (a cognition) and get vaccinated (an action) without feeling any autonomic arousal (no feeling). If you have some of the elements listed in the definition of emotion, but not all of them, do you have an emotion or not?

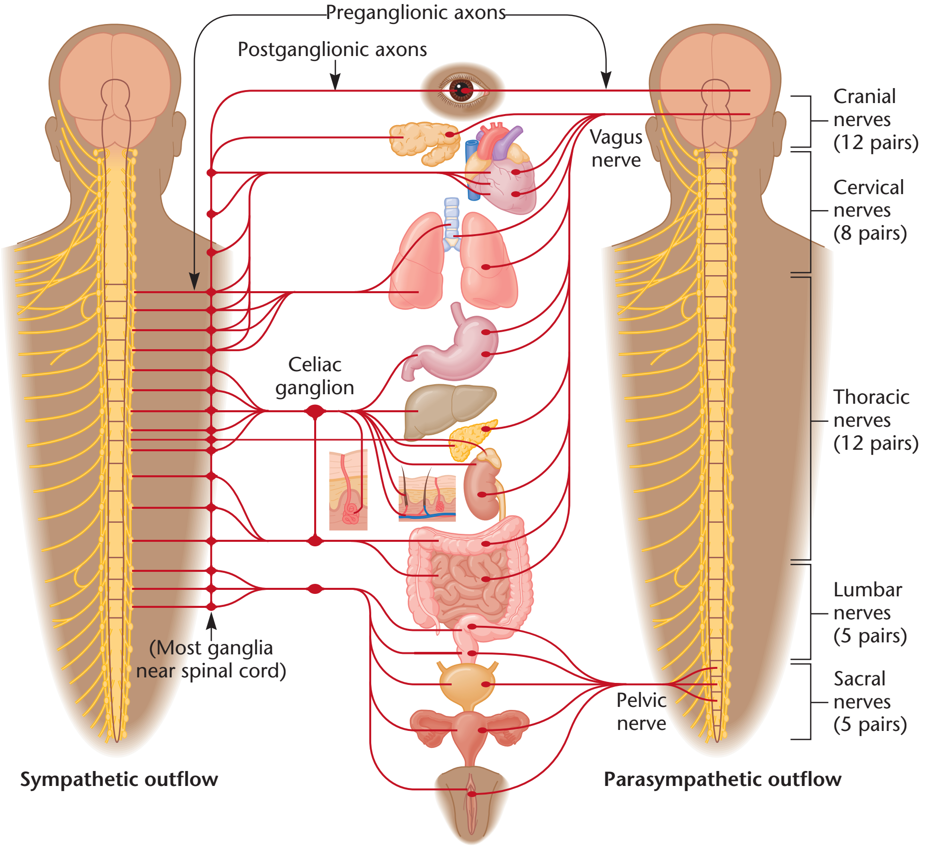
Emotion and Autonomic Arousal

Emotional situations arouse both the sympathetic and parasympathetic nervous systems. Figure 11.1 reviews the anatomy. Researchers had long recognized that the sympathetic nervous system stimulates certain organs, such as the heart, while inhibiting others, such as the stomach and intestines. Walter Cannon (1945) was the first to recognize the pattern: It stimulates organs important for vigorous "fight-or-flight" activities while inhibiting vegetative activities that can wait until later. The parasympathetic nervous system is the "rest and digest" system that saves energy and prepares for later needs.

Nearly all situations evoke a combination of sympathetic and parasympathetic arousal (Wolf, 1995). We think of danger as something that would elicit mostly sympathetic activity, but often it does not. If a small animal sees a potential predator at a great distance, it becomes alert, but motionless. (The predator is less likely to notice an immobile animal.) The little animal's heart rate *decreases*, by increased parasympathetic input. If the predator appears to notice, or if it comes closer, then the sympathetic nervous

Figure 11.1 The sympathetic and parasympathetic nervous systems

The autonomic nervous system receives sensory information from the organs and sends output to control the organs. The sympathetic system prepares the body for vigorous activity. The parasympathetic system conserves energy for later use.


Preganglionic axons
Postganglionic axons
Cranial nerves (12 pairs)
Vagus nerve
Cervical nerves (8 pairs)
Celiac ganglion
Thoracic nerves (12 pairs)
Lumbar nerves (5 pairs)
(Most ganglia near spinal cord)
Sacral nerves (5 pairs)
Pelvic nerve
Sympathetic outflow
Parasympathetic outflow

system takes over. We humans also become alert and cautious and decrease our heart rate when we are aware of a possible danger at a distance (Löw et al., 2015).

Stop & Check

1. Does seeing something dangerous activate mostly the sympathetic or parasympathetic nervous system?

See page 361 for the answer.

Is Physiological Arousal Necessary for Emotion?

In people with a condition called **pure autonomic failure**, the autonomic nervous system completely or almost completely ceases activity. The heart and other organs continue to function, but the nervous system no longer regulates them. People with this condition do not react

National Library of Medicine

Walter B. Cannon (1871–1945)

As a matter of routine I have long trusted unconscious processes to serve me. . . . [One] example I may cite was the interpretation of the significance of bodily changes which occur in great emotional excitement, such as fear and rage. These changes—the more rapid pulse, the deeper breathing, the increase of sugar in the blood, the secretion from the adrenal glands—were very diverse and seemed unrelated. Then, one wakeful night, after a considerable collection of these changes had been disclosed, the idea flashed through my mind that they could be nicely integrated if conceived as bodily preparations for supreme effort in flight or in fighting. (Cannon, 1945)

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to experiences with changes in heart rate, blood pressure, or sweating. They report "having" the same emotions as anyone else, and they have little difficulty identifying what emotion a character in a story would probably experience (Heims et al., 2004), but they feel their emotions less intensely than before (Critchley et al., 2001). Presumably, when they report experiencing emotions, they refer mainly to the cognitive aspect: "I'm angry, because this is a situation that calls for anger."

People with damage to the right somatosensory cortex have typical autonomic responses to emotional music but report little subjective experience. People with damage to part of the prefrontal cortex have weak autonomic responses but normal subjective responses (Johnsen et al., 2009). These results suggest that autonomic responses and subjective experience are not always closely connected.

Actions Alter Emotions

Physiological responses increase emotional intensity. If you watch a horror movie in a cold room, where the temperature caused you to shiver, you might rate the movie as scarier than you would have in a warmer room (Sugamura and Higuchi, 2015). It is easier to feel angry while standing (and therefore in a position to attack) than while lying in a more helpless position (Harmon-Jones and Peterson, 2009). Because perceptions of your body's actions contribute to your emotional feelings, psychologists describe emotions as "embodied"—that is, they depend on the body's responses.

According to the **facial-feedback hypothesis**, smiling may make you feel happier, and frowning may make you feel unhappier. Researchers could not test this hypothesis simply by telling people to smile or frown and then asking how they felt. To disguise their intention, they asked people to hold a pen with either the teeth or the lips. Try it: Holding a pen with your teeth almost forces a smile, and holding it with your lips prevents a smile, as in Figure 11.2. The first study reported that people holding a pen with their teeth were more likely to rate cartoons as being funny (Strack et al., 1988). Several attempts to replicate this result failed, but the difference depended on a detail of procedure: Unlike the original study, those replication attempts put a camera right in front of the person's face to be sure the pen was held correctly. When people face a camera, they tend to think about how they look on the camera, and it changes their reactions. A later study found that holding the pen in the teeth did increase amusement if no camera was present, but the effect disappeared with a camera (Noah et al., 2018). Similarly, getting people to sit up straight, by modifying the height of the chair and the desk, may also improve mood (Awad et al, 2021). Getting people to frown by attaching golf tees to their eyebrows and telling them to keep touching the tips of the tees may increase unpleasant feelings (Larsen et al., 1992). Laboratory studies have found support for the facial feedback hypothesis that is reasonably dependable, although it is a small effect (Coles et al., 2019).

Try It Yourself

Another way to alter facial expressions is to use botulinum toxin (Botox), which blocks transmission at nerve–muscle junctions. Physicians use Botox to paralyze the muscles for frowning and remove frown lines on people's faces. According to the facial-feedback hypothesis, making it difficult to frown should improve mood. In fact, a series of placebo-controlled studies found that Botox to the frown muscles relieves depression more powerfully than antidepressant medications generally do (Schulze et al., 2021). Given the small size of the facial feedback effect in laboratory studies, the reportedly large effect on depression is stunning. The explanation would possibly be that prolonging the effect over months is far more effective than the temporary effects in a laboratory.

Stop & Check

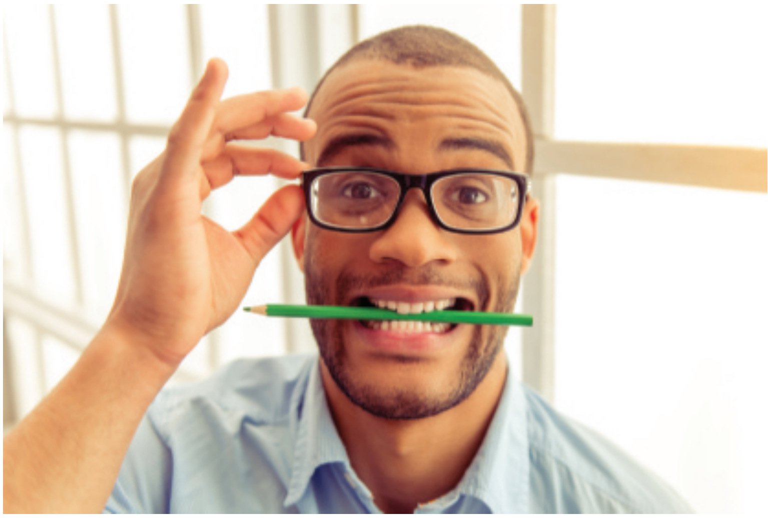
2. Observations on pure autonomic failure support which theoretical statement about emotions?

3. What is the relevance of Botox to the facial-feedback hypothesis?

See page 361 for the answer.

Figure 11.2 Effect of facial expression on emotion

Holding a pencil in your teeth, facilitating a smile, increases your probability of reporting amusement.



George Rudy/Shutterstock.com

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Basic Emotions or Continuous Dimensions

In the late 1800s and early 1900s, psychological researchers hoped to identify the elements of the mind, analogous to the elements of chemistry. They debated whether the psychological elements were thoughts, ideas, images, or something else. Before long, that quest seemed futile. Later psychologists hoped to find the elements of motivation, offering lists of the basic motivations. That pursuit led to such fascinating questions as whether breathing counts as just one motivation or two (inhaling and exhaling). Today, emotion is the only area in which many researchers still hope to identify the elements, the "basic" emotions. The alternative is to regard emotional experience in terms of continuous dimensions.

Brain Representations of Emotion

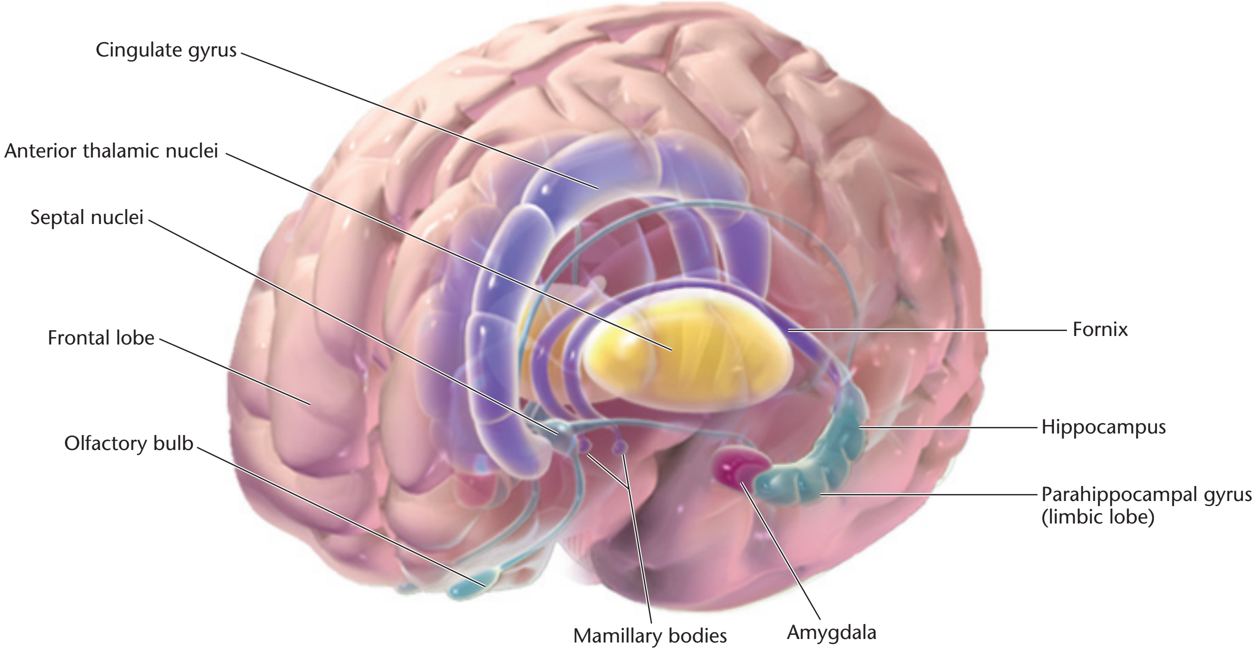
From a biological standpoint, much evidence favors dimensions. Heart rate and breathing rate increase with the intensity of an emotion, but they do not distinguish fear from anger, or any other pair of emotions. The same is true for other responses. You could not identify anyone's emotion by measuring autonomic activity (Lang, 2014).

Traditionally, the **limbic system**—the forebrain areas surrounding the thalamus—has been regarded as important for emotion (Figure 11.3). We consider part of it, the amygdala, in more detail later in this chapter. Much of the cerebral cortex also reacts to emotional situations. Researchers have used PET or fMRI techniques to identify brain areas that respond while people look at emotional pictures or listen to emotional stories. In Figure 11.4, each dot represents a research study that found significant activation of a cortical area associated with happiness, sadness, disgust, fear, or anger (Phan et al., 2002). The most salient point of this figure is the variability of locations for each emotion. The results apparently depend more on the details of procedure than on which emotion was targeted. The only emotion that seems to depend mostly on one brain area is disgust, which exhibits a link to the insula, a cortical area that is also important for taste (Verstaen et al., 2016). The best way to evoke dis-gust (literally, "bad taste") is to imagine something foul in your mouth.

Researchers found strong responses in the right-hemisphere junction between the temporal and parietal cortices while people watched an emotionally charged movie. No cell had responses that were specific to one emotion or another, such as fear or sadness, but researchers found three gradients, as depicted in Figure 11.5. One gradient represented pleasure vs. displeasure ("polarity" in the figure). Another gradient represented the intensity of the emotion. The researchers described the third gradient as "complexity," ranging from conflict at one pole to unambiguous emotion (usually fearful) at the other (Lettieri et al., 2019).

Figure 11.3 The limbic system

The limbic system is a group of structures in the interior of the brain. Here they are depicted as if the exterior of the brain were transparent.



(**Source:** Based on MacLean, 1949)

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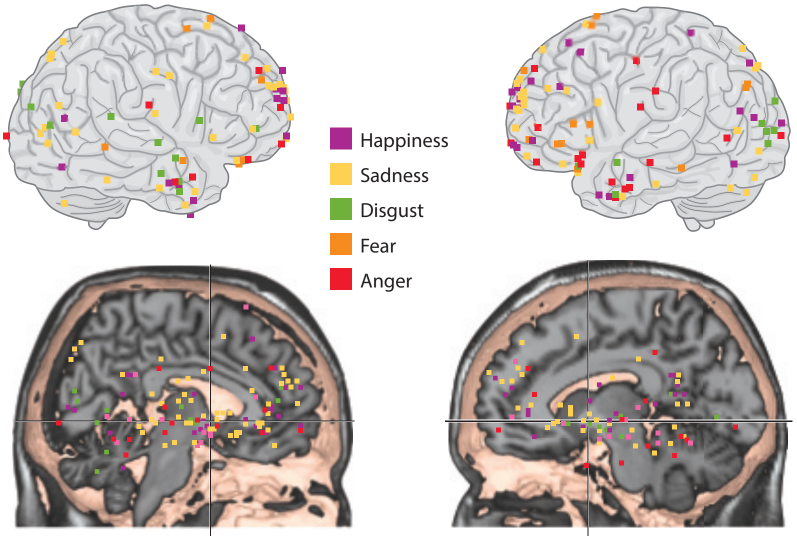
Figure 11.4 Brain areas associated with emotions

Each dot represents a study that found increased activity in a given brain area associated with the emotion designated by the color of the dot.



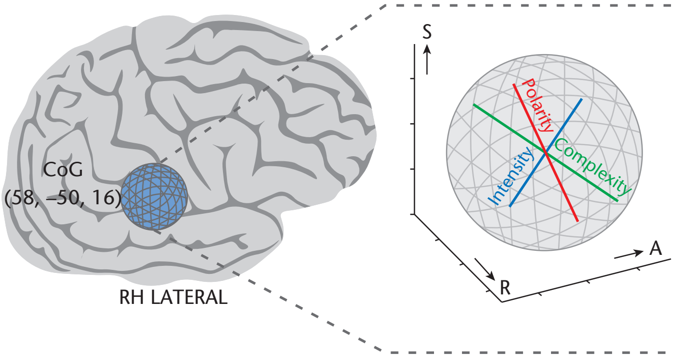
In short, these findings support the idea that brain responses are well described as dimensions of emotion rather than as discrete categories (Heller et al., 2013; Lindquist et al., 2012; Mueller et al., 2015).

Hemispheric Differences

Another important aspect of emotion is activation versus inhibition. Activity of the left hemisphere, especially its frontal and temporal lobes, relates to what Jeffrey Gray (1970) called the **behavioral activation system (BAS)**, marked by low to moderate autonomic arousal and a tendency to approach, which could characterize happiness or anger. Activity of right hemisphere, again mainly the frontal and temporal lobes, is associated with the **behavioral inhibition system (BIS)**. The BIS was initially described as responsible for withdrawal, but according to later research it is better described as inhibiting impulses and resolving conflict between drives (Gable et al., 2018). On average, people with greater activity in the frontal cortex of the left hemisphere tend to be happier and more extraverted. People with greater right-hemisphere activity tend to be more socially withdrawn, cautious, and prone to unpleasant emotions (Knyazev et al., 2002; Shackman et al., 2009; Urry et al., 2004). The hemispheres also differ in their contribution to perceiving others' emotions. In general, the right hemisphere is more active in perceiving emotions, especially negative emotions such as fear (Najt et al., 2013).

Figure 11.5 Representation of emotion as three gradients

At the temporo-parietal junction in the right hemisphere, cells represent polarity (pleasant vs. unpleasant), intensity, and complexity along three axes.



(**Source:** From Lettieri et al. (2019), Emotionotopy in the human right temporo-parietal cortex. Nat. Commun. 10, article 5568 ; Link for Reference: https://www.nature.com/articles/s41467-019-13599-z)

Stop & Check

4. What dimensions of emotion did researchers find in the temporo-parietal junction of the right hemisphere?

See page 361 for the answer.

Expressing Emotion

The main support for the idea of basic emotions has relied on consistency of facial expressions. In countries throughout the world, people have similar facial expressions for similar situations, such as weddings, fireworks, or sports competitions (Cowen et al., 2021). People who are blind since birth exhibit expressions of happiness, sadness, fear, pride, and shame that resemble those of sighted people (Eibl-Eibesfeldt, 1973; Valente et al., 2018). It is agreed that some emotional expressions are partly built-in, though capable of learned modification. The controversial issue is whether those expressions fall into a small number of discrete categories.

If presented with a set of faces, such as those in Figure 11.6, and given a list of emotion terms, most people in cultures throughout the world pair them up with greater-than-chance accuracy. However, this evidence is less than convincing. The faces used in most research, including those in Figure 11.6, were posed to try to maximize recognition. For spontaneous expressions, observers often perceive two or more emotions at a time, and observers' guesses do not always match the self-reports by the people in the photographs (Kayyal and Russell, 2013). The procedure of asking people to match the six faces to six labels exaggerates the accuracy. The procedure requires use of those six labels, even if an observer would have used some other label. Moreover, if you know five of them, you get the sixth one by process of elimination. Even if you know only one, you improve your guessing on the others. If you label the face at the upper left as "fear," and you know one of them has to be "surprise," you give that label to the face at the lower right, but if you had seen that face alone, you might have called it "fear." If you saw the expression in the lower center by itself, you might have called it anger instead of disgust (Pochedly et al., 2012).

Another problem: People recognize expressions from their own culture better than those from other cultures (Gendron et al., 2014). Young people in two cultures largely isolated from Western influences were able to recognize the expression for happiness at better than 50 percent accuracy, but they had low accuracy on other expressions, especially the expression intended to depict anger (Crivelli et al., 2016).

Furthermore, we rarely identify someone's emotion from facial expression alone. Participants in one study viewed photos of pro tennis players who had just won or lost a point in a difficult, high-stakes match (Figure 11.7). From photos of body posture, the observers could usually guess whether the player was happy (having won the last point) or sad (having just lost it). But from facial expression alone, the observers' guesses were close to chance levels (Aviezer et al., 2012). Another study also found that for

Figure 11.6 Facial expressions of emotion

Can you identify which face corresponds to happiness, sadness, fear, anger, disgust, and surprise? Check answer A on page 361.

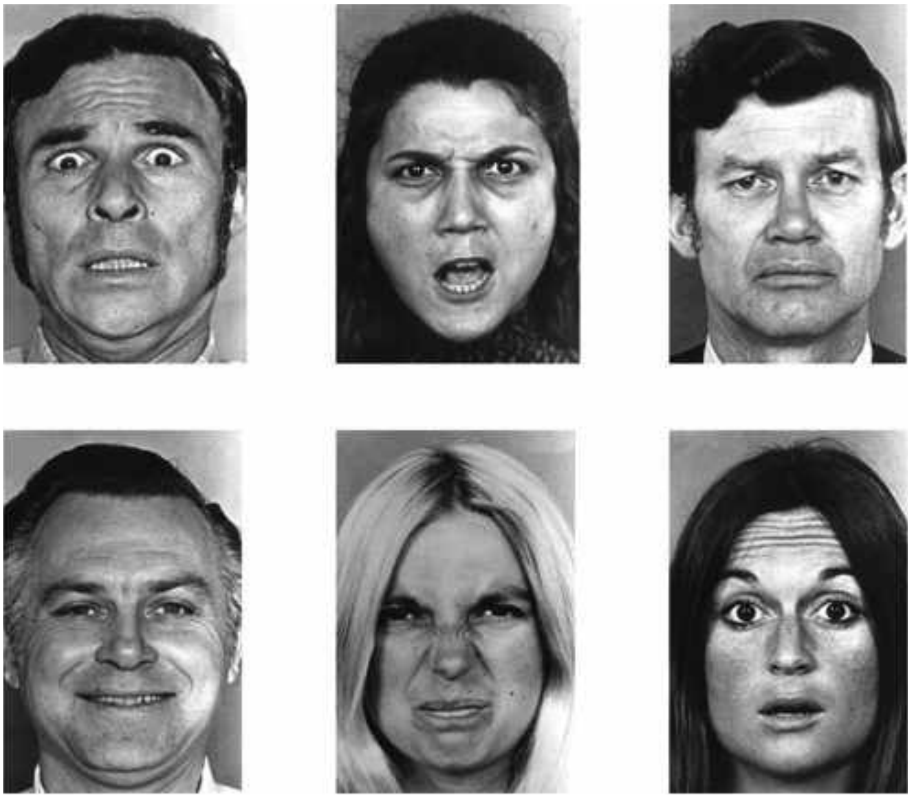


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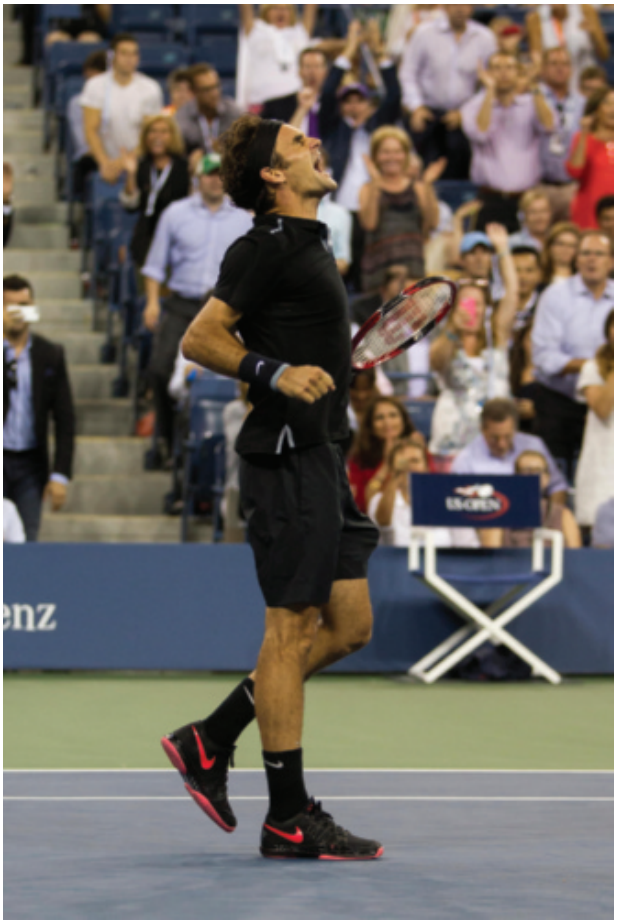
Figure 11.7 Emotional expressions in posture and face

Can you identify whether the player had just won or lost? Check answer B on page 361.



PCN Black/PCN Photography/Alamy Stock Photo

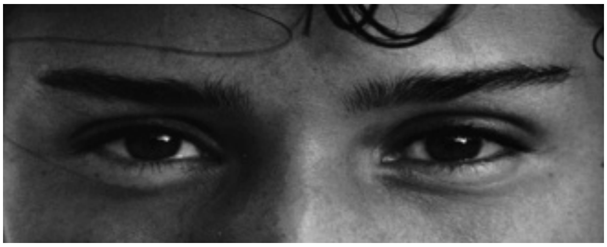
both children and adults, the expressions of intense pleasure appear similar to those for intense pain (Wenzler et al., 2016).

Finally, even if it were true that people could identify six emotions from facial expressions, that evidence would not demonstrate that we have precisely six emotions. People can also recognize with moderate accuracy the facial expressions of contempt, pride, sleepiness, and confusion (Keltner and Shiota, 2003; Rozin and Cohen, 2003; Tracy and Robins, 2004; Tracy, Robins, and Lagattuta, 2005

Just as people differ in almost everything else, they differ in their ability to recognize emotional expressions. On average, young adults are better than older people in this regard, and women are better than men (Olderbak et al., 2019). People with psychopathic tendencies are worse than average, as you might guess (Waller et al., 2019). Researchers measured people's ability to identify complex emotions from seeing just the eyes, as in Figure 11.8. Then they compared the results to brain measurements, based on MRI. The result was that successful identification of emotions correlated strongly with axons connecting the frontal cortex to the anterior temporal cortex (Coad et al., 2020). Previous research had found disruptions in that axon tract in several psychiatric conditions marked by poor social relationships. In short, details of brain anatomy have much to do with the ability to recognize emotional expressions.

Figure 11.8 An item to test recognition of facial expressions

Do these eyes express being playful, comforting, irritated, or bored? Check answer C on page 361.



Source: From Coad, B.M., Postans, M., Hodgetts, C.J., Muhlert, N., Graham, K.S., and Lawrence, A.D. (2020). Structural connections support emotional connections: Uncinate fasciculus microstructure is related to the ability to decode facial emotional expressions. *Neuropsychologia 145,* 106562, p. 4.

The alternative to basic emotions is to describe emotional experiences along one or more dimensions, such as pleasure to displeasure, and degree of arousal (Russell, 1980). One model is that what we label as emotions are cognitive elaborations (that is, our attributions) for feelings of pleasure or displeasure (Ortony, 2022).

Stop & Check

5. Why does the usual way of testing recognition of emotions overestimate accuracy?

6. What biological factor influences the ability to recognize people's emotional expressions?

See page 361 for the answer.

The Functions of Emotion

If we evolved the capacity to experience and express emotions, emotions must have served some adaptive function. What good do emotions do?

Sometimes the answer is clear. Fear alerts us to escape from danger. Anger directs us to attack an offender. Disgust tells us to avoid something that might cause illness. The adaptive value of happiness, sadness, embarrassment, and other emotions is more speculative, although psychologists have suggested plausible possibilities. Research has also found that emotions provide a useful guide when we need to make a quick decision.

Emotions and Moral Decisions

When we make important decisions, we pay much attention to how we think an outcome will make us feel. Consider the

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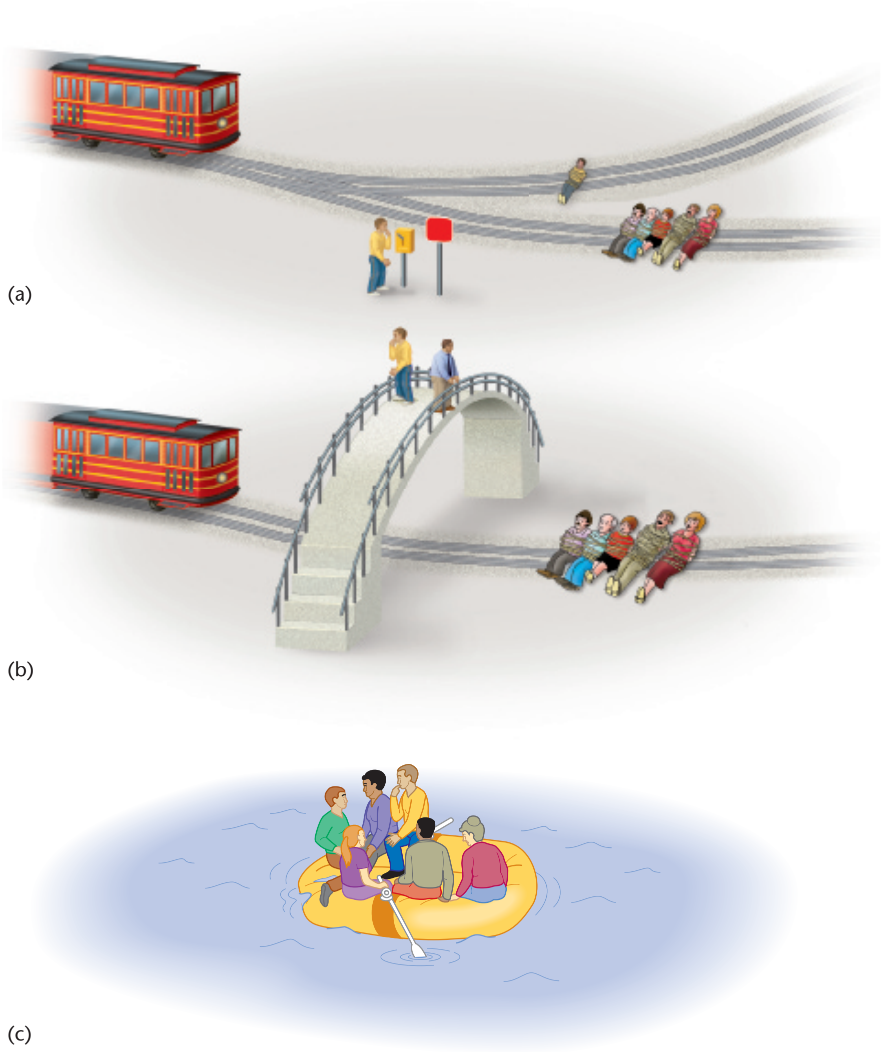
Figure 11.9 Three moral dilemmas

(a) Would you divert a runaway train so it kills one person instead of five? **(b)** Would you push someone off a footbridge so a runaway train kills him instead of five others? **(c)** Would you push someone off a sinking lifeboat to save yourself and four others?



following moral dilemmas, of which Figure 11.9 illustrates three:

The Trolley Dilemma. A runaway trolley is headed toward five people on a track. The only way you can prevent their death is to switch the trolley onto another track, where it will kill one person. Should you pull the switch?

The Footbridge Dilemma. You are standing on a footbridge overlooking a trolley track. A runaway trolley is headed toward five people on a track. The only way you can prevent their death is to push a heavy-set stranger off the footbridge and onto the track so that he will block the trolley. Would it be right to push him?

The Lifeboat Dilemma. You and six other people are on a lifeboat in icy waters, but it is overcrowded and starting to sink. If you push one of the people off the boat, the boat will stop sinking and the rest of you will survive. Would it be right to push someone off? Would it make a difference if that person already had a serious illness?

The Hospital Dilemma. You are a surgeon, and five of your patients will die soon unless they get organ transplants. Each needs the transplant of a different organ, and you haven't been able to find organ donors for any of them. A nurse bursts into your office: "Good news! A visitor to the hospital has just arrived, who has the same tissue type as all five of your patients! We can kill this visitor and use the organs to save the other five!" Would it be right to do so?

In each of these dilemmas, you can save five people (including yourself in the lifeboat case) by killing one person. However, although that may be true logically, the decisions

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do not feel the same. Most people say (hesitantly) that it is right to pull the switch in the trolley dilemma, fewer say yes in the footbridge and lifeboat dilemmas, and almost no one endorses killing one person to save five others in the hospital dilemma. Brain scans demonstrate that contemplating these dilemmas activates brain areas known to respond to emotions, including parts of the prefrontal cortex and cingulate gyrus (Greene et al., 2001). When you contemplate these situations, you react emotionally because you identify with the person whose suffering and death you might cause by your action, and that feeling is especially intense if you imagine putting your hands on someone rather than just flipping a switch. People with the strongest autonomic arousal are the least likely to decide to kill one to save five others (Cushman et al., 2012; Navarrete et al., 2012).

When you make a moral decision, you compare the utilitarian aspect (for example, five people die versus one person dies) and the emotional aspect (how you would feel about performing the action). According to fMRI studies, certain brain areas become active when people contemplate just the utilitarian aspect, other areas become active when they contemplate just the emotional aspect, and the ventromedial part of the prefrontal cortex becomes active when they compare the utilitarian and emotional aspects to make a decision (Hutcherson et al., 2015; Shenhav and Greene, 2014). What would happen after damage to the ventromedial prefrontal cortex? People with such damage tend to make decisions without much consideration of the emotional impact (Yu et al., 2020). When confronted with the moral dilemmas we just discussed, they are more likely than average to choose the utilitarian option of killing one to save five (Ciaramelli et al., 2007; Koenigs et al., 2007).

Would you flip the switch to kill one and save five if the one to be killed was your mother or your daughter? Almost everyone shudders and says of course not, but some people with damage to the ventromedial prefrontal cortex calmly say it would be okay to do so (Thomas et al., 2011). If you thought you could kill someone you hated and get away with it, would you do it? Some people with ventromedial prefrontal cortex damage say yes, especially if the damage occurred early in life (Taber-Thomas et al., 2014). Evidently, they do not imagine feeling sad after the death of a loved one and they do not imagine feeling guilty after committing murder.

The most famous case of prefrontal damage is that of Phineas Gage. In 1848, an explosion sent an iron rod through Gage's prefrontal cortex. Amazingly, he survived. During the next few months, he exhibited impulsive behavior and poor decision making, two common symptoms of prefrontal damage. Unfortunately, the reports about his behavior don't provide as much detail as we would like. Over the years, with multiple retellings, people exaggerated the meager facts available (Kotowicz, 2007).

We know more about a modern case. Antonio Damasio (1994) examined a man with prefrontal cortex damage who expressed almost no anger, sadness, or pleasure. Contrary to the idea that unemotional means logical, he made bad decisions that cost him his job, his marriage, and his savings. When tested in the laboratory, he successfully predicted the probable outcomes of various decisions. For example, when asked what would happen if he cashed a check and the bank teller handed him too much money, he knew the probable consequences of returning it or walking away with it, but he admitted, "I still wouldn't know what to do" (Damasio, 1994, p. 49). He knew that one action would win him approval and another would get him in trouble, but he apparently did not anticipate that approval would feel good and trouble would feel bad. Any choice requires consideration of values and emotions—how we think one outcome or another will make us feel. In Damasio's words, "Inevitably, emotions are inseparable from the idea of good and evil" (Damasio, 1999, p. 55).

Stop & Check

7. What brain activity influences decisions on moral dilemmas?

See page 361 for the answer.

Module 11.1 | In Closing

Emotions and the Nervous System

Although we regard emotions as internal subjective states, they are fundamentally biological. They are embodied. Biological research sheds light on important questions about the psychology of emotions. For example, it supports the idea of that emotions occur along dimensions instead of distinct categories. Brain damage studies suggest that emotional reactions are often a useful quick guide to appropriate moral actions.

Summary

1. Most attempts to define emotion include several aspects including cognition, feelings, and action. However, distinguishing between emotion and motivation is difficult and perhaps pointless. **352**
2. The sympathetic nervous system readies the body for emergency fight-or-flight activities. The parasympathetic

nervous system conserves energy and prepares for the future. **352**

3. People with impaired autonomic responses continue to report emotional experiences, but the feeling aspect is weaker than before. **353**
4. Feedback from facial expressions modifies emotional feelings. This effect is small for short term feedback, but may be larger after a long-term intervention. **354**
5. Apparently no emotion corresponds to activity in a single brain area. In the temporo-parietal junction, cells represent several aspects of emotion along three continuous gradients. **355**
6. Activation of the frontal and temporal areas of the left hemisphere is associated with approach and the behavioral activation system. The corresponding areas of the right hemisphere are associated with the behavioral inhibition system that resolves conflicts among impulses through inhibition. **356**
7. People recognize others' emotions partly by facial expressions. Individual differences in the ability to recognize facial expressions correlate with connections between the frontal cortex and the anterior temporal cortex. **357**
8. Damage to the ventromedial prefrontal cortex in many cases impairs the ability to anticipate emotional consequences, and it thereby alters responses to moral dilemmas. **360**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

behavioral activation system (BAS)	**356**
behavioral inhibition system (BIS)	**356**
facial-feedback hypothesis	**354**
limbic system	**355**
pure autonomic failure	**353**

Thought Question

People with pure autonomic failure experience weaker than average emotional feelings. What kind of people might experience stronger than average emotions?

Stop & Check Answers

1. It depends. If the danger is distant, it activates the parasympathetic system, but if it is close, it activates the sympathetic system.
2. The statement that intensity of emotional feeling depends on autonomic responses.
3. Botox to the frowning muscles makes it harder to frown, and decreases depression, as the facial-feedback hypothesis predicts.
4. Polarity (pleasant vs. unpleasant), intensity, and complexity.
5. The usual procedure is to ask people to match six faces to six labels. After you identify one or more for sure, you improve your chance of guessing other ones correctly.
6. People with better connections between the frontal cortex and the anterior temporal cortex tend to be better at recognizing facial expressions.
7. The ventromedial prefrontal cortex compares utilitarian (cognitive) information and the expected emotional outcome. People with damage in this area tend to put less weight on the emotional aspects.

Answers to Questions in the Text

Question A, page 357: From left to right: fearful, angry, sad, happy, disgusted, surprised

Question B, page 358: Roger Federer had just won the match. If you answered correctly, were you responding to his posture or his facial expression?

Question C, page 358: playful

Module 11.1 | End-of-Module Quiz

1. Who first identified the sympathetic nervous system with fight-or-flight activities?
   - **a.** William James
   - **b.** Walter Cannon
   - **c.** Wilhelm Wundt
   - **d.** John Watson
2. Pure autonomic failure most strongly impairs which aspect of emotions?
   - **a.** Facial expressions
   - **b.** Intensity of feelings
   - **c.** Ability to distinguish pleasure from displeasure
   - **d.** Ability to distinguish fear from anger
3. The facial feedback hypothesis makes which of these predictions?
   - **a.** Stimulating certain brain areas elicits specific emotions.
   - **b.** Increased frowning will decrease happiness.
   - **c.** Children have to learn to recognize other peoples' emotional expressions.
   - **d.** Psychotherapy can change the way people express negative emotions.

4. Researchers found three gradients of response in the right temporo-parietal junction as people watched an emotional movie. What were those dimensions?
   - **a.** Polarity, intensity, complexity
   - **b.** Happiness, sadness, anger
   - **c.** Happiness, fear, anger
   - **d.** Cognition, arousal, feeling

5. Which brain area is associated with the behavioral activation system and a tendency to approach?
   - **a.** The right hemisphere
   - **b.** The left hemisphere
   - **c.** The amygdala
   - **d.** The hippocampus

6. Certain research studies overestimated people's ability to recognize facial expressions of emotion because they used which research method?
   - **a.** fMRI
   - **b.** Matching questions
   - **c.** Short-term memory
   - **d.** True-false questions

7. Ability to recognize emotional expressions correlates with which of the following?
   - **a.** Diameter of the corpus callosum
   - **b.** Connections between the frontal cortex and the anterior temporal cortex
   - **c.** Ratio of neurons to glia cells in the amygdala and the hypothalamus
   - **d.** Density of axons connecting the receptors of the retina to cells in the thalamus

8. Damage to the ventromedial prefrontal cortex increases which tendency in making decisions?
   - **a.** Greater conformity to the majority opinion
   - **b.** Longer delays in making decisions
   - **c.** More choices based on emotional feelings
   - **d.** More utilitarian choices

Answers: 1b, 2b, 3b, 4a, 5b, 6b, 7b, 8d.

Module 11.2

Attack and Escape Behaviors

Learning Objectives

After studying this module, you should be able to:

4. Describe what is known about the genetics of aggression.
5. Evaluate the roles of testosterone, serotonin, and cortisol in aggressive behavior.
6. Discuss the role of the amygdala in emotional processing.
7. Describe biological aspects of anxiety disorders.
8. Comment on methods of relieving anxiety.

Have you ever observed a cat play with a rat or mouse before killing it? It kicks, bats, tosses, shakes, and carries the rodent. Is the cat sadistically tormenting its prey? No. A cat usually goes for a quick kill if the rodent is small and inactive or if the cat has been given drugs that lower its anxiety. The same cat withdraws altogether if confronted with a large, menacing rodent. In intermediate situations, the cat mixes attack and escape behaviors in ways that look to us like play (Adamec et al., 1980; Biben, 1979; Pellis et al., 1988).

It is no coincidence that we describe the sympathetic nervous system as the fight-or-flight system. Anger and fear are closely related both behaviorally and physiologically.

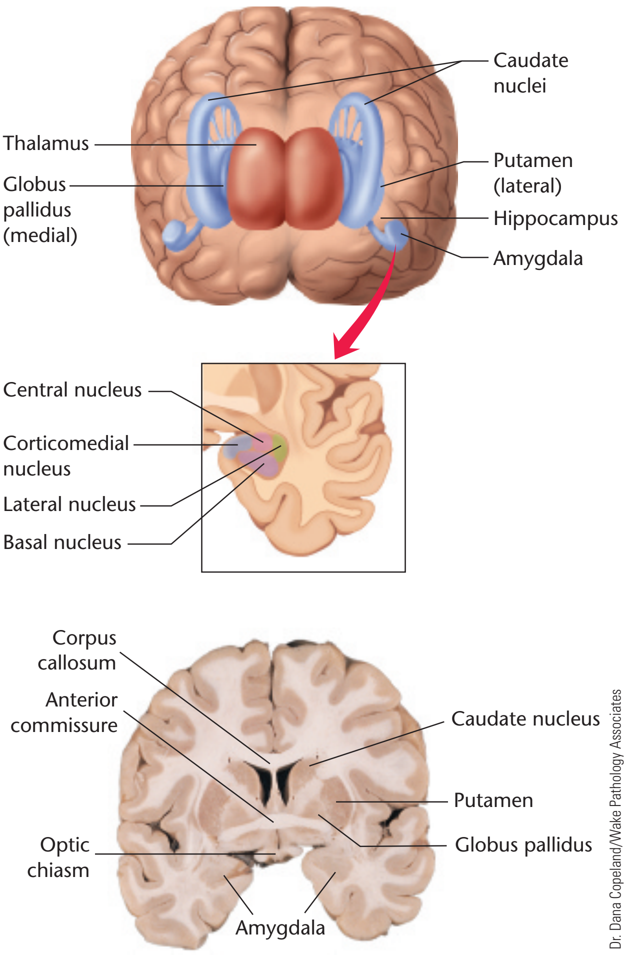
Attack Behaviors

Attack behavior depends on the individual as well as the situation. If a hamster intrudes into another hamster's territory, the home hamster sniffs the intruder and eventually attacks, but usually not at once. Suppose the intruder leaves, and a little later, another hamster intrudes. The home hamster attacks faster and more vigorously than before. The first attack enhances home hamster's readiness to attack against any intruder for the next 30 minutes or more (Potegal, 1994). It is as if the first attack gets the hamster in the mood to fight. During that period, activity builds up in the corticomedial area of the **amygdala** (Figure 11.10), and as it does so, it increases the hamster's probability of attacking (Potegal et al., 1996; Potegal et al., 1996). Something similar happens in people: If you hold a toddler's arm to prevent him or her from playing with a toy, the result is often screaming or other signs of anger. If you do it again 30 seconds later, the anger is more rapid and more intense (Potegal et al., 2007). (*Do not* try it yourself. It's unkind.)

Attack behaviors also vary among species. Some people have argued that it is "in our animal nature" to be violent, at least for males. Well, maybe and maybe not. Of our nearest animal relatives, chimpanzees in some African

Figure 11.10 Location of amygdala in the human brain

The amygdala, located in the interior of the temporal lobe, receives input from many cortical and subcortical areas.



(**Source:** [a] Based on Hanaway et al., 1998; Nieuwenhuys et al., 1988; [b] Photo courtesy of Dr. Dana Copeland)

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troops are extremely, even murderously aggressive, but chimps in other troops are much less aggressive, and bonobos rarely fight at all (de Waal, 2022). People are capable of unspeakable cruelty, but cooperative behavior is vastly more common (Bregman, 2019).

Genetic and Environmental Influences

As with almost anything else in psychology, individual differences in aggressive, violent, or antisocial behavior depend on both heredity and environment. Environmental factors that increase the probability of violent behavior include an abusive childhood, witnessing violence between one's parents, living in a violent neighborhood, exposure to lead and other harmful chemicals, and heavy use of alcohol or other drugs.

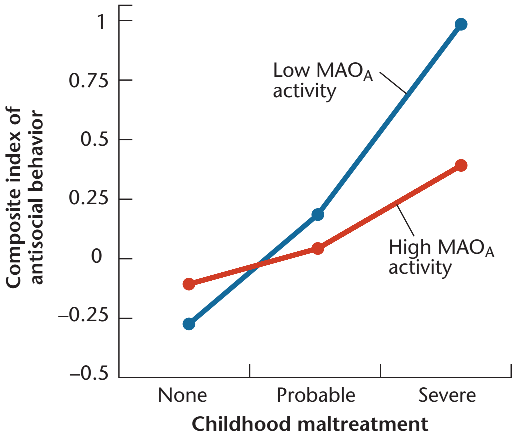
What about heredity? Twin studies generally indicate significant heritability, but the results vary for many reasons, including how the researchers measure aggression (Veroude et al., 2016). Some studies have measured real-world criminal violence, some have measured relatively trivial aggressive behavior in a laboratory setting, and some have relied on answers to questionnaires. Many studies failed to distinguish between offensive and defensive violence. Furthermore, heritability of antisocial behavior is higher in middle-class neighborhoods than in the most impoverished neighborhoods (Burt et al., 2016). The interpretation is that extremely bad environment can elicit antisocial behavior in almost anyone. Someone who engages in violent behavior despite a more privileged upbringing might have a genetic predisposition.

A study of prisoners with a history of extreme impulsive violence found that 123 of the 281 men studied had one or more rare genetic variants linked to brain functioning (Vevera et al., 2019). Of the rare genetic variants linked to a high probability of violence, the one most thoroughly studied is a gene causing deficiency of **monoamine oxidase A (MAOA)**. After a neuron releases serotonin, dopamine, or norepinephrine, most of it returns to the neuron via reuptake. At that point monoamine oxidases break down some of it, preventing excess accumulation. A deficiency MAOA increases the build-up of serotonin inside neurons, evidently altering early brain development in a way that increases the risk of antisocial behavior, especially in males (Kolla and Bortolato, 2020). Because the MAOA gene is on the X chromosome, males are far more likely than females to have the variant form of the gene without a normal form to compete with it. Research with mice also demonstrates a link between a genetic deficiency of MAOA and later aggressive behavior (Mentis et al., 2021).

Even people lacking this rare mutant have genetic variations in their production of MAOA. A highly influential report found that a lower-activity form of the MAOA gene increased violent behavior *only* in people who had a seriously troubled childhood environment, such as being physically abused or watching parents fight (Caspi et al., 2002). This result is fascinating because of its apparent demonstration of an interaction between genetics and environment. Figure 11.11 illustrates the report. Since then, most but not all studies have found a similar effect, and many factors influence the results (Nilsson et al., 2018). For example, a positive supporting figure can mitigate the harm caused by abusive childhood experiences.

Figure 11.11 Genes, environment, and antisocial behavior in men

The *y* axis represents a complex score combining several types of measurement. Higher scores indicate more aggressive behaviors.



(**Source:** From "Role of genotype in the cycle of violence in maltreated children," by A. Caspi, et al., *Science, 297,* 851–854. © 2002 AAAS.)

Stop & Check

8. What does MAOA do?

9. What relationship did Caspi et al. (2002) report between the enzyme MAO$_A$ and antisocial behavior?

See page 374 for the answer.

Testosterone

Most fighting in the animal kingdom is by males competing for mates, and their aggressive behavior depends on testosterone. In all cultures, males are more likely to fight than females, commit more violent crimes, and shout more insults at one another. Moreover, young adult males, who have the highest testosterone levels, have the highest rate of aggressive behaviors and violence. Females can be aggressive toward one another also, but more often by gossip, shaming, or ostracism than by physical injury (Archer, 2000, de Waal, 2022). However, in many animal species, a mother becomes very aggressive in defense of her young. You do not want to get between a mother grizzly bear and her cubs.

The natural assumption is that testosterone increases violent behavior, and yet, for humans the evidence is

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weaker than we might expect. Although the difference in aggressive behavior between young adult males and everyone else probably relates to testosterone, the results are less impressive if we compare people within an age group, or one set of prisoners to another. In those cases, the correlation between baseline testosterone level and aggressive behavior is statistically significant (if we study a large enough group), but low (less than 0.1). The amount that testosterone increases in an emotional situation correlates a little higher with aggression, but still less than 0.2 (Geniole et al., 2020).

A few experiments have administered testosterone by absorption through mouth, nose, or skin. The effect on aggressive behavior has been unimpressive for most men (Carre and Robinson, 2020; Geniole et al., 2019, 2020). Several interesting results occurred when investigators administered testosterone to women. Because females start with low testosterone levels, an increase might produce more effect than it does in males. In one study, testosterone increased the amount of time females spent looking at angry faces (Terburg et al., 2012). In another study, testosterone increased female's dominance behavior (Masson et al., 2021). In yet another, women were asked to make judgments about visual stimuli, either individually or in pairs. Testosterone did not alter accuracy of individuals' judgments, but it reduced the accuracy of pairs' decisions (Wright et al., 2012). The women became more likely to argue instead of collaborating, and one of them—not necessarily the more correct one—dominated the decision. This result fits with other research finding that committees work more harmoniously if they include a high percentage of females—of course, females who hadn't just been given testosterone (Wooley et al., 2010).

Stop & Check

10. Why might the effects of testosterone administration be stronger for women than for men?

See page 374 for the answer.

Serotonin Synapses and Aggressive Behavior

Several lines of evidence link impulsive, aggressive behavior to low serotonin release. Let's examine some of this evidence.

Nonhuman Animals

Much of the earliest evidence came from studies on mice. Luigi Valzelli (1973) found that isolating male mice for 4 weeks increased their aggressive behavior and decreased their serotonin **turnover**, the amount that neurons released and replaced. When neurons release serotonin, they reabsorb most of it and synthesize enough to replace the amount that washed away. Measuring the amount that washed away measures turnover, and therefore the amount that had been released. Researchers measure serotonin turnover by the concentration of **5-hydroxyindoleacetic acid (5-HIAA)**, serotonin's main metabolite, in the cerebrospinal fluid (CSF). Measuring the amount in the blood or urine is simpler but less accurate.

Comparing genetic strains of mice, Valzelli and his colleagues found that social isolation lowered serotonin turnover by the greatest amount in the strains that reacted with the greatest amount of fighting after social isolation (Valzelli and Bernasconi, 1979). Other methods of decreasing serotonin turnover also increase aggressive behavior (Audero et al, 2013). Serotonin activity is lower in juvenile rodents than in adults, and fighting is more frequent in the juveniles (Taravosh-Lahn et al., 2006).

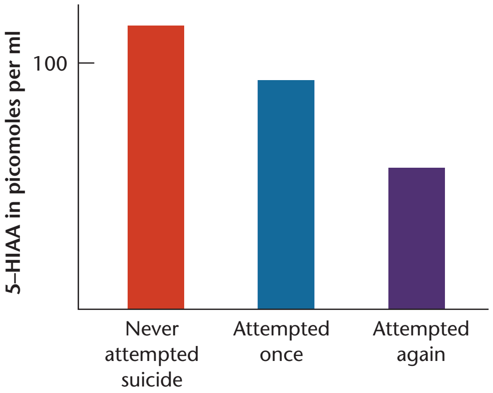
Humans

Many early studies reported low serotonin turnover in people with a history of violent behavior, including people convicted of arson and other violent crimes (Virkkunen et al., 1987) and people who attempt suicide by violent means, as illustrated in Figure 11.12 (Fanelli and Serretti, 2019; Roy et al., 1989). Follow-up studies on people released from prison found that those with lower serotonin turnover had a greater probability of further convictions for violent crimes (Virkkunen et al., 1989; Virkkunen et al., 1996).

Later studies found less consistent effects. One reason is that some studies measured actual behavior, whereas others relied on answers to questionnaires (Duke et al., 2013). Also, many studies relied on serotonin measurements from the blood, which correlates poorly with serotonin in the brain (Runions et al., 2019). Overall, low serotonin turnover does appear to correlate with human aggressive behavior, but not strongly.

Figure 11.12 Levels of 5-HIAA in the CSF of people with depression

Measurements for the suicide-attempting groups were taken after the first attempt. Low levels of 5-HIAA indicate low serotonin turnover.



(**Source:** Based on results of Roy et al., 1989)

Testosterone and Cortisol

According to the **dual-hormone hypothesis**, aggressive behavior relates to facilitation by testosterone and inhibition by the hormone cortisol. During periods of stress and anxiety, the adrenal gland secretes cortisol, which promotes cautious behavior to conserve energy. Cortisol increases during anxiety and decreases during anger (Kazén et al., 2012). Many studies have tested the hypothesis that aggressive behavior occurs mostly when testosterone levels are high and cortisol low. A study of adolescents found aggressive behavior correlated with high levels of testosterone and low levels of cortisol in their hair (Grotzinger et al., 2018). Hair samples indicate the average levels of those chemicals, as opposed to an instantaneous level. Still, a review of the literature found only a low level of support for the dual-hormone hypothesis (Dekkers et al., 2019).

Studying human aggressive behavior is difficult. Many studies rely on self-reports, which are not always accurate. Ethical constraints prevent experiments that might induce people to strike each other. In a typical experiment, people play a game in which they can take credits away from each other, and experimenters observe how much one of them retaliates against the other, offering varying forms of retaliation. The people are in separate rooms without seeing each other, just imagining each other, and usually the "other person" is not really a person, but a computer. This type of behavior is a long way from serious violence, and maybe that is why most experiments find only weak relationships to testosterone or other chemicals.

Stop & Check

11. What does a measurement of 5-HIAA indicate?

12. How do testosterone and cortisol affect aggressive behavior?

See page 374 for the answer.

Fear and Anxiety

Do we have any built-in, unlearned fears? Yes, at least one: A sudden loud noise causes newborns to arch their backs, briefly extend their arms and legs, and cry. This reaction is called the *Moro reflex.* Whether to call this behavior fear is a matter of opinion. (The alternative is "distress.") After infancy, a loud noise elicits the closely related **startle reflex**: Auditory information from the cochlear nucleus in the medulla goes directly to an area in the pons that tenses the muscles, especially the neck muscles. Tensing the neck muscles is important because the neck is so vulnerable to injury. Information reaches the pons within 3 to 8 ms after a loud noise, and the full startle reflex occurs in less than two-tenths of a second (Yeomans and Frankland, 1996). The startle reflex is widespread throughout the animal kingdom.

Although you don't have to learn to fear loud noises, your current mood or situation modifies your reaction. Your startle reflex is more vigorous if you are already tense. People with post-traumatic stress disorder have an enhanced startle reflex (Grillon et al., 1998). So do people who report much anxiety, even if they don't qualify for a psychiatric diagnosis (McMillan et al., 2012). Variations in the startle reflex correlate well enough with anxiety that we can use the startle reflex to measure anxiety. Don't underestimate the power of that statement. Research on other types of emotion is hampered by the difficulty of measurement. The suitability of the startle reflex to measure anxiety means that we can use it with not only with humans, but also with laboratory animals to explore the brain mechanisms.

Joe McBride/The Image Bank/Getty Images

People's choices of activities depend in part on how easily they develop anxiety.

Role of the Amygdala in Rodents

Extensive research with rodents has demonstrated the importance of the amygdala for fear and anxiety. The brain pathways are the same in humans (Kuhn et al., 2020), but the research can go into more detail with rodents. In research with rodents, psychologists first measure the startle response to a sudden loud noise. They repeatedly pair some stimulus with shock, and then they present that stimulus

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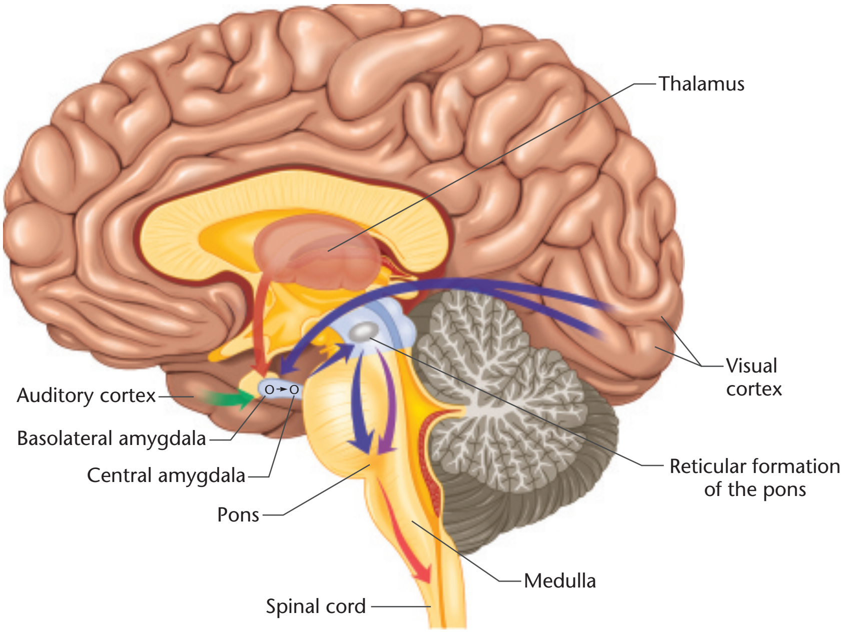
Figure 11.13 Amygdala and learned fears

The central amygdala receives sensory input from the lateral and basolateral amygdala. It sends output to the central gray area of the midbrain, which relays information to a nucleus in the pons responsible for the startle reflex. Damage anywhere along the route from the amygdala to the pons interferes with learned fear or safety that would otherwise modify the startle reflex.



before the loud noise and determine how much it increases the startle response. A control group is tested with a stimulus that was not paired with shock. Results of such studies consistently indicate that the stimulus paired with shock becomes a fear signal, and that presenting it just before a loud noise enhances the startle response. Conversely, a stimulus previously associated with something pleasant, or with the absence of danger, becomes a safety signal that decreases the startle reflex (Schmid et al., 1995).

Investigators determined that the amygdala (Figures 11.10 and 11.13) is important for modifying the startle reflex, and for learned fears in general. A rat with damage to the amygdala, or with its connections to the hindbrain, still exhibits a normal startle reflex, but signals of danger or safety do not modify the reflex (Hitchcock and Davis, 1991).

An odd parasite has evolved a way to exploit the consequences of amygdala damage (Berdoy et al., 2000). *Toxoplasma gondii* is a protozoan that infects many mammals but reproduces only in cats. Cats excrete the parasite's eggs in their feces, thereby releasing them into the ground. Rats or mice that burrow in the ground can become infected with the parasite. When the parasite enters a rodent, in many cases (about 50 percent) it migrates to the brain where it damages the amygdala. The rodent then fearlessly approaches a cat, increasing the likelihood that the cat will eat the rat and that the parasite will find its way back into a cat!

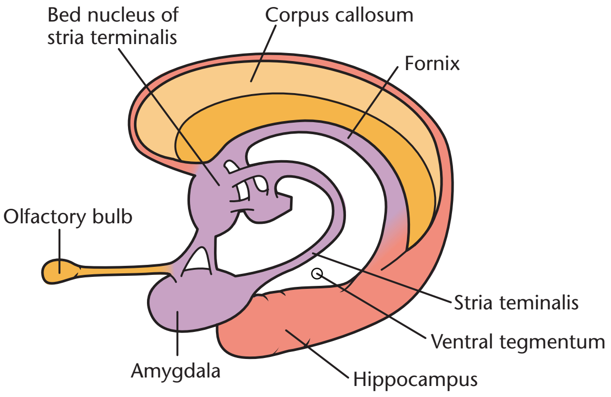
Researchers have worked out many of the connections responsible for the amygdala's effects. At the sight of danger, the superior colliculus responds rapidly, sending a message via the thalamus to the amygdala, which immediately prepares defensive actions (Kragel et al., 2021). The amygdala also exchanges information with the cerebral cortex in ways that generate slower, more deliberate responses.

By stimulating or damaging parts of laboratory animals' amygdala, researchers found one path through the amygdala that is responsible for fear of pain, another path for fear of predators, and yet another for fear of aggressive members of one's own species (Gross and Canteras, 2012). Also, one part of the amygdala controls changes in breathing, another controls avoidance of potentially unsafe places, and another controls learning which places are safest (Kim et al., 2013). The path from the amygdala responsible for freezing in the presence of danger is separate from the path controlling changes in heart rate (Tovote et al., 2016; Viviani et al., 2011), and it is also separate from the path for fleeing to escape (Fadok et al., 2017). Yet another path from the amygdala inhibits appetite during intense fear (Yang et al., 2021). This diversity of mechanisms is relevant to psychological theories of emotion: They suggest that what we call fear is not a single thing, but a conglomerate of separate aspects.

The amygdala is important for learning to fear a particular stimulus, but that is not the only type of fear. If a

Figure 11.14 The bed nucleus of the stria terminalis

The bed nucleus is critical for long-term adjustments of anxiety, whereas the amygdala is responsible for fear of individual items. The stria terminalis is a set of axons connecting its bed nucleus to the amygdala.



rat has received shocks after a particular stimulus in a particular cage, it learns to fear the stimulus, but it also becomes more fearful in general, everywhere and always. The same is true for humans. If you have been attacked, you fear anything associated with that attack, but also you become more fearful overall. Your brain has decided, "This is a dangerous world. I need to be alert for threats." This long-term, generalized emotional arousal depends on a brain area called the **bed nucleus of the stria terminalis** (Duvarci et al., 2009; Toufexis, 2007). The stria terminalis is a set of axons that connect the bed nucleus to the amygdala, as depicted in Figure 11.14. The efficacy of the stria terminalis largely influences people's attention to possible threats (Koller et al., 2019).

Stop & Check

13. What does amygdala research tell us about the concept of fear?
14. What aspect of fear depends on the bed nucleus of the stria terminalis?

See page 374 for the answer.

Studies in Monkeys

The effect of amygdala damage in monkeys was first described in classic studies early in the 1900s and is known as the *Klüver-Bucy syndrome,* from the names of the primary investigators. Monkeys with this syndrome are tame and placid. They attempt to pick up lighted matches and other objects that they ordinarily avoid. They display less than the normal fear of snakes or dominant monkeys (Kalin et al., 2001). They have impaired social behaviors, largely because they don't seem to learn which monkeys to approach with caution. Like rats with amygdala damage, monkeys with such damage are impaired at learning what to fear (Kazama et al., 2012).

Response of the Human Amygdala to Visual Stimuli

Studies with fMRI find that the human amygdala responds strongly when people look at photos that arouse fear or at photos of faces expressing fear or anger (Mattavelli et al., 2014). The amygdala can also respond to pleasant stimuli if a task requires attention to pleasant stimuli, but even then, the response is never as great as it is to unpleasant stimuli (Stillman et al., 2015). The amygdala's response to a frightened face emerges in the remarkably fast time of just 74 milliseconds (ms) after presentation of the photo (Méndez-Bértolo et al., 2016), faster than the response by the fusiform gyrus and other areas responsible for facial recognition. You respond to the fear in someone's face before you recognize whose face it is.

Contrary to what we might guess, the amygdala responds most strongly when a facial expression is difficult to interpret. Consider angry and frightened faces. It is usually easy to interpret an angry face looking straight at you, but a fearful face looking straight at you can be puzzling. Frightened people stare at whatever is frightening them, and so the only time people stare at you with a fearful expression is when they are afraid of *you!* Your amygdala responds more strongly to expressions that are harder to interpret—a fearful expression directed toward you, of an angry face directed away from you (Adams et al., 2003; Adams and Kleck, 2005) (Figure 11.15).

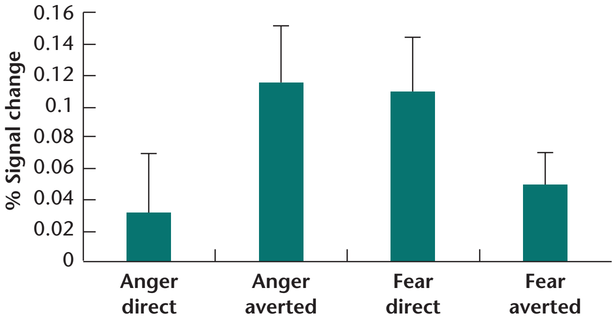
Stop & Check

15. Given that the amygdala becomes more active when an expression is harder to interpret, can you explain why it does not respond strongly to happy faces?

See page 375 for the answer.

Figure 11.15 Amygdala response and direction of gaze

The amygdala responds more strongly to an angry face directed away from you and to a frightened face directed toward you.



(**Source:** From Adams, R. B. et al. "Effects of gaze on amygdala sensitivity to anger and fear faces," *Science,* 2003, 300:1536. Reprinted with permission from AAAS/Science Magazine.)

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Damage to the Human Amygdala

With laboratory animals, researchers can intentionally damage the amygdala to see the effects. With humans, they rely on damage that occurs spontaneously. When people experience a stroke that damages the amygdala and surrounding areas, at least in one hemisphere, they are impaired in certain ways. They can classify photos as pleasant versus unpleasant about as well as anyone else, but they experience less arousal from viewing unpleasant pictures (Berntson et al., 2007). They have no problem with the cognitive aspect of unpleasant emotions, but they lack much of the feeling aspect.

People with the rare genetic *Urbach-Wiethe disease* accumulate calcium in the amygdala until it wastes away, without much damage to surrounding structures. Like the monkeys with Klüver-Bucy syndrome, they are impaired at processing emotional information and learning what to fear. This condition is rare, and the behavioral effects vary (Hortensius et al., 2017).

Much of the research deals with a woman known by her initials, SM, who describes herself as fearless, and certainly acts that way. When she viewed 10 clips from the scariest movies the researchers could find, she reported feeling only excitement, not fear. Researchers took her to an exotic pet store. Despite insisting that she hates snakes and spiders, she was happy to hold a snake (Figure 11.16), and the staff repeatedly had to restrain her from touching or poking the tarantulas and venomous snakes. When the researchers took her to a "haunted house," she led the way without hesitation, venturing down dark hallways. When people dressed as monsters jumped out, other people in the group screamed, but SM laughed, curiously poked one of the monsters, and scared the monster!

Figure 11.16 SM, a woman with amygdala damage, holds a snake at an exotic pet store

Although she said she hates snakes, she was curious to hold this one and wanted to touch the others, including venomous ones.

(**Source:** From Feinstein, J. S., Adolphs, R., Damasio, A., and Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Current Biology, 21*, 34–38 with permission from Elsevier.)

Here is another example of her fearlessness: Suppose someone you don't know approaches you, face to face. How close could that person come before you began to feel uncomfortable? Most Americans stand about 2 feet (0.7 m) away from another person, but SM's preferred distance is about half that. When a man unknown to her followed the experimenters' instruction to approach her so close that their noses touched, she stood still and reported no discomfort (Kennedy et al., 2009). (She did say she wondered whether they were "up to something.")

SM's fearlessness is dangerous to her. She has been held up at gunpoint and knifepoint and has been physically assaulted repeatedly. She plunges into dangerous situations without the caution other people would exhibit. When she describes these events, she remembers feeling angry, not afraid (Feinstein et al., 2011). She can drive a car, however, avoiding accidents. She knows what is dangerous in an intellectual way, even though she does not react to it emotionally.

The only event known to trigger her fear is breathing 35 percent carbon dioxide, which leaves a person gasping for breath. She and two others with Urbach-Wiethe disease reacted to concentrated CO_2 with a panic attack. The difference from other fear stimuli is that carbon dioxide affects the body directly, rather than by information that the amygdala would have to interpret. However, although all three people said it was a terrible experience and they thought they were going to die, they all agreed to go through the experience again the following week, and they did not think about it again during that delay (Feinstein et al., 2013). Apparently, the amygdala is important for imagining the fear.

SM and other people with Urbach-Wiethe disease often are unable to recognize the emotional expressions in faces, especially expressions of fear or disgust (Boucsein et al., 2001). When SM was asked to draw faces depicting certain emotions (Figure 11.17), she made good drawings of most expressions but had trouble drawing a fearful expression, saying that she did not know what such a face would look like. When the researcher urged her to try, she drew someone crawling away with hair on end, as cartoonists often indicate fear (Adolphs et al., 1995). She was given a series of statements and asked how each one would make someone feel. To statements such as "I think you are being followed," she seldom guessed that they would feel afraid (Cardinale et al., 2021).

Why do SM and others with amygdala damage have trouble identifying facial expressions of fear? At first, the assumption was that they do not feel fear and therefore cannot understand the expression. But then Ralph Adolphs and his colleagues observed that SM focuses almost entirely on the nose and mouth of each photograph. Also in everyday life, she seldom makes eye contact, looking at the mouth instead (Spezio et al., 2007). The amygdala automatically directs attention toward emotionally significant stimuli, even without your awareness (Amting et al., 2010; Burra et al., 2013; Peck et al., 2013; Pishnamazi et al., 2016), but someone lacking an amygdala doesn't have this automatic tendency. Suppose you are looking at a computer screen,

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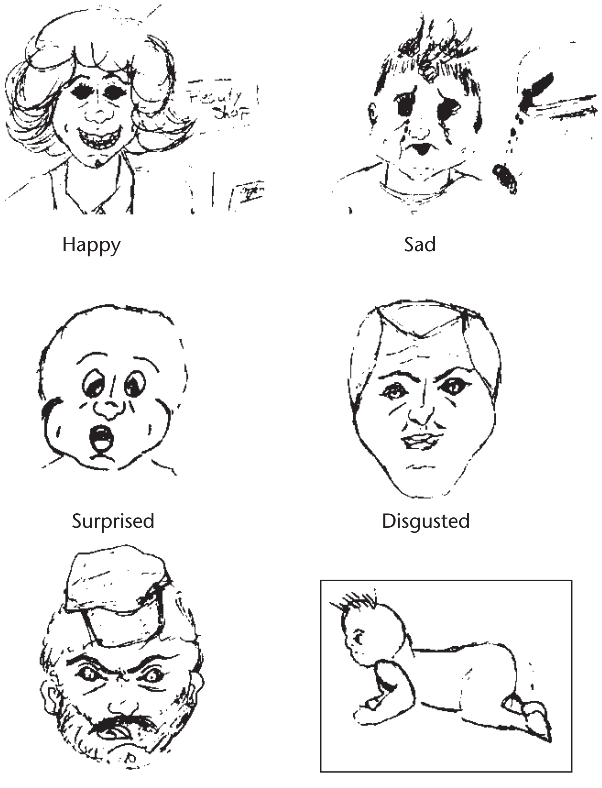
Figure 11.17 Drawings by SM, who has a damaged amygdala

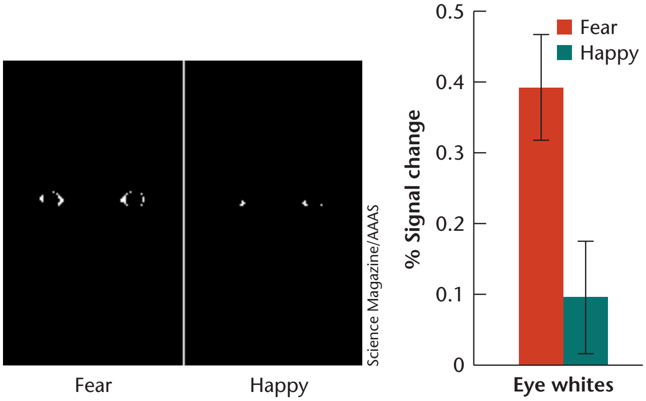
She at first declined to draw a fearful expression because, she said, she could not imagine it. When urged to try, she remembered that cartoons depict frightened people with their hair on end.


Happy
Sad
Surprised
Disgusted
Angry
Afraid

(**Source:** From "Fear and the human amygdala," by R. Adolphs, D. Tranel, H. Damasio, and A. Damasio, *Journal of Neuroscience, 15,* 5879–5891. Copyright © 1995 by Oxford University Press. Reprinted by permission.)

Figure 11.18 Eye expressions for fear and happiness

The eye whites alone enable most people to guess that the person on the left was feeling afraids.



(**Source:** From "Human amygdala responsivity to masked fearful eye whites," by P. J. Whalen et al., *Science*, 2004, *306*, 2,061. Reprinted by permission from AAAS/Science magazine.)

and a face is flashed on the screen. Almost instantaneously, you would move your gaze to focus on the eyes, especially if the face was showing fear (Gamer and Büchel, 2009). SM is willing to make eye contact, but eyes don't automatically attract her attention, as they do for most other people (Kennedy and Adolphs, 2010). When researchers asked her to focus on the eyes, she recognized fearful expressions (Adolphs et al., 2005). Seeing the eyes is particularly important for recognizing fear. People express happiness with the mouth, but they express fear mainly with the eyes (Morris et al., 2002; Vuilleumier, 2005). Figure 11.18 depicts only the whites of the eyes of people expressing fear (left) and happiness (right). Most people recognize the fear expression, but not the happy expression, from the eyes alone (Whalen et al., 2004).

These observations suggest an alternative interpretation of the function of the amygdala. Instead of being responsible for *feeling* fear or other emotions, evidently it is responsible for detecting emotional information, evaluating its relevance, and directing attention to it (Pishnamazi et al., 2016).

Stop & Check

16. Why do people with amygdala damage have trouble recognizing expressions of fear?

See page 375 for the answer.

Individual Differences in Amygdala Response and Anxiety

Most people's tendency toward anxiety remains consistent over time. Most infants with an inhibited temperament

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Ralph Adolphs

Will a better understanding of the social brain lead to a better understanding of social behavior? And can such knowledge ultimately be used to help our species negotiate and survive in the vastly complex social world it has helped create? To approach such questions, social neuroscientists will need to establish dialogues with other disciplines in the social and behavioral sciences, and to be highly sensitive to the public consequences of the data they generate. (Adolphs, personal communication)

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develop into shy, fearful children and then into shy adults who demonstrate an enhanced amygdala response to the sight of any unfamiliar face (Beaton et al., 2008; Schwartz et al., 2003). They also have an increased probability of developing anxiety disorders. Research with monkeys has traced an inhibited temperament to partly heritable over-activity of both the amygdala and the bed nucleus of the stria terminalis (Claus, 2019; Kenwood and Kalin, 2021; Oler et al., 2010).

In one study, college students carried a device that beeped at unpredictable times each day for 28 days, asking them to record their current emotional state. A year later the students came into a laboratory for the second part of the study, when an fMRI recorded their amygdala response to brief presentations of frightening pictures. The amygdala responses correlated highly with the number of unpleasant emotions they had recorded the previous year (Barrett et al., 2007). Presumably they recorded so many unpleasant emotions because they were biologically predisposed to react strongly.

Researchers measured Israeli soldiers' amygdala responses to briefly flashed unpleasant photos, at the time of induction into the army. Later the soldiers reported their responses to combat stress. Soldiers with the greatest amygdala response at the start reported the greatest amount of combat stress (Admon et al., 2009). Again, it appears that amygdala response relates to fear reactivity.

In addition to the amygdala, anxiety depends on cortical areas that help people cope with threatening information. An effective way to cope is *reappraisal*—reinterpreting a situation as less threatening. If you lose your job, you might tell yourself, "This will prompt me to look for a new job. It might turn out for the best." If you hear a sudden noise that might be a gunshot, you could decide it was probably a car backfiring. Reappraisal and similar methods of suppressing anxiety depend on top-down influences from the prefrontal cortex to inhibit activity in the amygdala (Marek et al., 2013; Moscarello and LeDoux, 2013). A study of police recruits found that those with higher activation in the prefrontal cortex were less likely than average to develop post-traumatic stress disorder after a traumatic experience (Kaldewaij et al., 2021).

Stop & Check

17. What does the evidence suggest about biological bases for anxiety disorders?

See page 375 for the answer.

Anxiety Disorders

What is the right amount of anxiety? It depends. On Caribbean islands with few predators, one species of lizards explores its environment freely. On nearby islands with an aggressive predator, lizards of the same species evolved cautious behaviors, avoiding the ground where they might be attacked (Lapiedra et al., 2018).

For humans, too, intense, constant anxiety makes sense if you live in a war zone or if you were recently attacked. Extreme anxiety is a disorder only if your anxiety seems excessive for your circumstances. **Panic disorder** is characterized by periods of anxiety and occasional attacks of rapid breathing, increased heart rate, sweating, and trembling—in other words, extreme arousal of the sympathetic nervous system—without an apparent reason. During a panic attack, people gasp for breath, worry that they are suffocating, and experience great anxiety (Klein, 1993). An important part of the disorder is frequent fear of the next panic attack. The fear of fear itself can become incapacitating. Panic disorder is more common in women than in men and declines as people grow older (Shen et al., 2007; Swoboda et al., 2003).

If you ever have a panic attack and you want to calm yourself, or if you want to decrease your heart rate for any other reason, here is something you can try. People have a little-known reflex. If you close your eyelids and press gently on your eyes, you can decrease your heart rate (Gillespie et al., 1926). This works much better for some people than others. Of course, if you wear contact lenses, you should remove them first.

Try It Yourself

Why are some people especially prone to anxiety? Stressful experiences are a major part of the story, and early stresses can increase reactions to later stresses. Stress aggravates anxiety in many ways. One of them is that repeated stresses overexcite the amygdala and thereby damage mitochondria, producing abnormalities in synaptic transmission (Duan et al., 2021).

A genetic predisposition contributes to anxiety disorders, although no common gene controls much of the variance. A study of more than sixteen thousand U.S. army soldiers found evidence for a genetic variant associated with anxiety disorders in people of European ancestry, but that gene had no significant effect for those of African or Latin American descent (Hettema et al., 2020).

Panic disorder occurs in about 15 percent of people with *joint laxity*, commonly known as being "double-jointed" (able to bend the fingers backward farther than usual). Even when people with joint laxity do not have panic disorder, they tend to have stronger than average fears (Bulbena et al., 2004; Bulbena et al., 2006).

Panic disorder relates to activity in both the hypothalamus and the amygdala. Panic disorder is associated with decreased activity of the neurotransmitter GABA and increased levels of orexin. Orexin increases wakefulness, activity, and eating. We might not have guessed that it would also increase anxiety, but it does. Axons releasing orexin all start in the hypothalamus, but they extend to many brain targets and exert a variety of effects. Acute stressful events stimulate orexin neurons that increase heart rate, breathing rate, and blood pressure, all of which relate to anxiety (Abreu et al., 2020). Drugs that block orexin receptors block panic responses (Johnson et al., 2015).

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People have long recognized that many soldiers returning from battle are prone to prolonged anxiety and distress. Long ago, people called the condition *battle fatigue* or *shell shock*. Today, we call it **post-traumatic stress disorder (PTSD)**, marked by frequent distressing recollections (flashbacks) and nightmares about the traumatic event, avoidance of reminders of it, and vigorous reactions to sudden noises (Yehuda, 2002). PTSD also occurs after other horrendous experiences, such as experiencing sexual assault or watching someone else get hurt. Increased anxiety after a traumatic experience is normal. However, not everyone who endures a trauma develops PTSD, and we cannot predict who will get PTSD based on the severity of the trauma or the intensity of the person's initial reaction (Harvey and Bryant, 2002; Shalev et al., 2000).

The humor publication *The Onion* once published an article about "pretraumatic stress disorder" that people developed by watching the news on television. Although this was intended as humor, psychologists found that it actually happens: Some soldiers develop mild symptoms similar to PTSD during preparation for deployment, and these soldiers are more likely than the others to develop serious symptoms after actual war experiences (Berntsen and Rubin, 2015).

PTSD relates to alterations in brain anatomy. Most people with PTSD have a smaller than average hippocampus. Is that difference a result of PTSD, or does it show a predisposition by people who already had a smaller hippocampus? Probably both are true. Investigators found cases of monozygotic twins in which one had developed PTSD as a soldier in the Vietnam war, and the other had not been in the war and did not have PTSD. On average, the soldiers with the most severe PTSD symptoms had the smallest hippocampus, and so did their twin who had not been in the war (Gilbertson et al., 2002). Two other studies found that people with the smallest hippocampus were the least likely to recover quickly from PTSD (Rubin et al., 2016; van Rooij et al., 2015). However, a similar study of twins found that the right hippocampus was eleven percent smaller in twins with PTSD than in those without (Bremner et al., 2021). Together, these results suggest that having a smaller than average hippocampus may increase the risk of PTSD, and that traumatic experiences may decrease the size even further.

Another point about PTSD: A study compared Vietnam War veterans who suffered injuries that produced various kinds of brain damage. Of those whose damage included the amygdala, *none* experienced PTSD. Of those with damage elsewhere in the brain, 40 percent experienced PTSD (Koenigs et al., 2008). Apparently, the amygdala, which is so important for emotional processing, is essential for the extreme emotional impact that contributes to PTSD. Supporting this conclusion, two people with severe epilepsy centered in the temporal cortex underwent surgery that removed the right amygdala. In both cases, the surgery relieved the epilepsy, and in both cases the people had PTSD before the surgery, but the symptoms greatly decreased afterward (Bijanki et al., 2020).

Stop & Check

18. What neurotransmitter abnormalities are common in people with panic disorder?

19. What conclusion emerges from studies of twins, one with PTSD and the other without it?

See page 375 for the answer.

Relief from Anxiety

People have many ways to cope with anxiety—social support, reappraisal of the situation, exercise, distraction, gaining a sense of control over the situation, and so forth. Here we consider the options for biological interventions.

Pharmacological Relief

People with excessive anxiety sometimes seek relief through medications. The most common *anxiolytic* (anti-anxiety) drugs are the **benzodiazepines** (BEN-zo-die-AZ-uh-peens), such as diazepam (trade name Valium), chlordiazepoxide (Librium), and alprazolam (Xanax). Benzodiazepines bind to the **GABA_A receptor**, which includes a site that binds GABA as well as sites that modify the sensitivity of the GABA site (Figure 11.19). The brain also has other kinds of GABA receptors, with different behavioral effects.

At the center of the GABA_A receptor is a chloride channel. When open, it permits chloride ions (Cl^-) to cross into the neuron, hyperpolarizing the cell or at least counteracting any sodium entering the cell through excitatory synapses. Surrounding the chloride channel are four units, each containing one or more sites sensitive to GABA. Benzodiazepines bind to sites on three of those four units (labeled α in Figure 11.19). When a benzodiazepine molecule attaches, it bends the receptor so that the GABA binds more easily (Zhu et al., 2018).

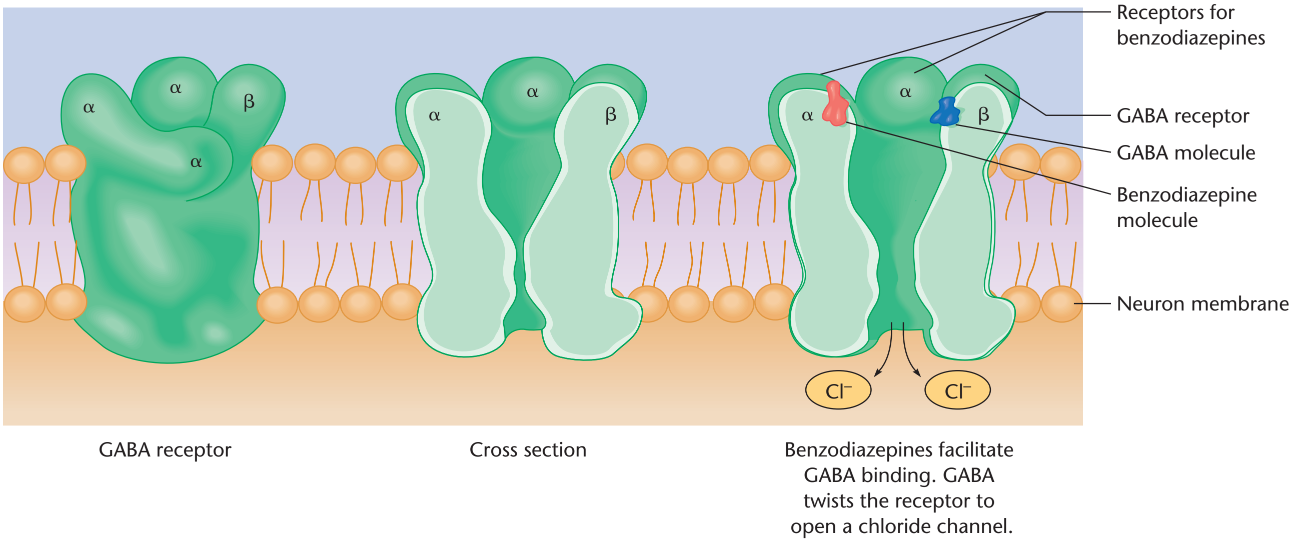
Benzodiazepines exert their anti-anxiety effects by facilitating inhibition in the amygdala, hypothalamus, midbrain, and other areas. A minute amount of benzodiazepines injected directly into a rat's amygdala decreases learned shock-avoidance behaviors (Pesold and Treit, 1995), relaxes the muscles, and increases social approaches to other rats (Sanders and Shekhar, 1995). Benzodiazepines provide relief from anxiety disorders, generally without major side effects other than a risk of addiction after prolonged use (Offidani et al., 2013).

An unfortunate aspect of benzodiazepines is that they are extremely stable chemically. They pass through the urine intact, mostly pass through a waste treatment plant intact, and accumulate in lakes and rivers, where they alter the eating and social behavior of resident fish (Brodin et al., 2013).

Another possible treatment has emerged, based on preliminary data (Reiff et al., 2020). The drug 3,4-methylenedioxymethamphetamine, mercifully abbreviated MDMA, often known as "ecstasy," is an abused drug with effects on serotonin, dopamine, norepinephrine, and oxytocin synapses. Studies on mice found that MDMA enhances extinction of

Figure 11.19 The GABA$_A$ receptor complex

Of its four receptor sites sensitive to GABA, the three alpha sites are also sensitive to benzodiazepines.


α
α
β
α
α
α
β
α
α
β
Receptors for benzodiazepines
GABA receptor
GABA molecule
Benzodiazepine molecule
Neuron membrane
Cl⁻
Cl⁻
GABA receptor
Cross section
Benzodiazepines facilitate GABA binding. GABA twists the receptor to open a chloride channel.

(**Source:** Based on Guidotti et al., 1986)

fear memories, and fMRI studies with humans demonstrated that it decreases the amygdala's response to unpleasant images. In one study, people took the drug during two eight-hour psychotherapy sessions, three weeks apart (Marseille et al., 2020). In another study, patients with PTSD had three psychotherapy sessions with MDMA, spread out over 18 weeks. In both cases most patients demonstrated significant improvement for months (Mitchell et al., 2021). These results suggest that this drug may create a period when someone can reconsider traumatic experiences while remaining in a less distressed mood. Although the early results are promising, more research is needed before this treatment can be widely recommended. Also note that the procedure is time-intensive for both the patient and the therapist, and therefore expensive.

Stop & Check

20. When benzodiazepines facilitate GABA, what happens at the postsynaptic neuron's membrane?

See page 375 for the answer.

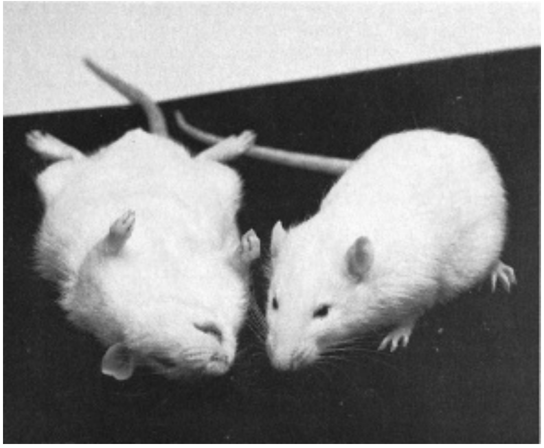
Alcohol and Anxiety

Alcohol also reduces anxiety through effects on GABA receptors. Alcohol promotes the flow of chloride ions through the GABA$_A$ receptor complex by binding strongly at a special site found on only certain GABA$_A$ receptors (Glykys et al., 2007). An experimental drug known as Ro15-4513 blocks the effects of alcohol on GABA receptors (Suzdak et al., 1986), thereby preventing the effects of alcohol on motor coordination, its depressant action on the brain, and its ability to reduce anxiety (Becker, 1988; Hoffman et al., 1987; Ticku and Kulkarni, 1988) (Figure 11.20).

Could Ro15-4513 be useful as a "sobering-up" pill or as a treatment for people who want to stop drinking alcohol? Hoffmann-La Roche, the company that discovered the drug, concluded that it would be too risky. People who relied on the pill might think they were sober enough to drive home when they were not. Also, giving such a pill to combat alcohol use disorder would probably backfire. Because people with problematic alcohol use drink to get drunk, a pill that decreased their feeling of intoxication would probably lead them to drink even more.

Figure 11.20 Two rats that were given the same amount of alcohol

The rat on the right was later given the experimental drug Ro15-4513. Within 2 minutes, its performance and coordination improved significantly.



National Institute of Mental Health

Module 11.2 | In Closing

Doing Something about Emotions

Anger and anxiety are important. People with excessive anxiety typically want to control it. People with excessive anger may or may not want to control it, but other people would certainly like them to control it. As of now, biological interventions are moderately effective for anxiety, but not for anger or violence. As research advances, we may someday face more questions about the extent to which we want to control emotions biologically … either our own or someone else's.

Summary

1. An experience that gradually provokes an attack leaves an individual more ready than usual to attack again. **363**
2. Aggressive behavior relates to both genetic and environmental influences. Most evidence supports the hypothesis that a gene decreasing the activity of monoamine oxidase A increases aggressive behavior mainly among people who had abusive experiences in childhood. **364**
3. Aggressive behavior in humans correlates with increased testosterone levels and decreased cortisol, but the correlations are weak, partly because of the difficulty of measuring aggressive behavior. **366**
4. Enhancement of the startle reflex indicates anxiety or learned fears. **366**
5. The amygdala is critical for increasing or decreasing the startle reflex, and for learned fears. **366**
6. Several parts of the amygdala control different responses to a danger signal, implying that fear is not a unitary event. **367**
7. The human amygdala responds strongly to stimuli that evoke strong emotional processing. **368**
8. People with damage to the amygdala fail to focus their attention on stimuli with important emotional content and seldom experience fear or anxiety. **369**
9. Anxiety disorders correlate with strong responses of the amygdala or weak inhibition by the prefrontal cortex. **371**
10. On average, people with PTSD tend to have a smaller hippocampus compared to those without PTSD. Studies have found both that a small hippocampus predisposes to PTSD, and that traumatic experiences may potentially decrease the size of the hippocampus. **372**
11. Anti-anxiety drugs decrease fear by facilitating the binding of the neurotransmitter GABA to the GABA_A receptors. **372**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

amygdala **363**
bed nucleus of the stria terminalis **368**
benzodiazepines **372**
dual-hormone hypothesis **366**
GABA_A receptor **372**
5-hydroxyindoleacetic acid (5-HIAA) **365**
monoamine oxidase A (MAOA) **364**
panic disorder **371**
post-traumatic stress disorder (PTSD) **372**
startle reflex **366**
turnover **365**

Thought Questions

1. Much of the play behavior of a cat can be analyzed into attack and escape components. Do you think the same may be true for children's play?
2. People with amygdala damage approach other people indiscriminately instead of trying to choose people who look friendly and trustworthy. What might be a possible explanation?

Stop & Check Answers

8. After reuptake of serotonin or one of the catecholamines to the presynaptic cell, the enzyme MAOA breaks down some of the excess molecules into an inactive form.
9. According to the report by Caspi and associates, a combination of serious maltreatment during childhood and lower levels of MAO_A increased antisocial behavior.
10. Men already have enough testosterone that the amount administered might not significantly alter their behavior.
11. Measurements of 5-HIAA, a metabolite of serotonin, indicates how much serotonin has been released and replaced.
12. Testosterone tends to increase aggressive, dominant behaviors. Cortisol tends to inhibit impulsive behaviors, including aggression. The research so far with humans finds only a weak effect of each.
13. What we call fear is not a single thing, but a combination of independent reactions.
14. It is responsible for long-term changes in emotional arousal and anxiety.

15. Smiling faces are easy to interpret!

16. They fail to make eye contact.

17. Some people are predisposed to anxiety disorders either because of increased responsiveness of the amygdala and associated areas, or because of less ability of the prefrontal cortex to suppress anxiety responses.

18. Low levels of GABA and increased release of orexin occur in people with panic disorder.

19. A smaller than average hippocampus is both a risk factor and a result of PTSD.

20. Chloride ions enter more readily.

Module 11.2 | End-of-Module Quiz

1. What is known about the genetics of violent behavior in humans?

- **a.** Many rare genetic variants can increase violent behavior.
- **b.** A gene on the Y chromosome is strongly linked to violent behavior.
- **c.** Two recessive genes combine their effects to produce violent behavior.
- **d.** Violent behavior in humans depends entirely on environment, not genetics.

2. How does the gene for the less active form of the enzyme MAOA affect the probability for aggressive behavior?

- **a.** Increased probability, regardless of environment
- **b.** Decreased probability, regardless of environment
- **c.** Increased probability for someone who was abused in childhood
- **d.** Increased probability for someone who lived in a middle-class neighborhood

3. Aggressive behavior correlates with low turnover of which neurotransmitter?

- **a.** Serotonin
- **b.** Norepinephrine
- **c.** Dopamine
- **d.** Glutamate

4. What chemical in the cerebrospinal fluid indicates the amount of serotonin turnover in the brain?

- **a.** Monoamine oxidase A
- **b.** Dopamine
- **c.** 5-HIAA
- **d.** Cortisol

5. According to the dual-hormone hypothesis, aggressive behavior correlates with what?

- **a.** Increased testosterone and increased cortisol
- **b.** Increased testosterone and decreased cortisol
- **c.** Increased serotonin and increased cortisol
- **d.** Increased serotonin and decreased cortisol

6. Why do we know more about the brain mechanisms of anxiety than we do about other emotions?

- **a.** Clinical psychologists have greater interest in anxiety than in other emotions.
- **b.** Anxiety depends on brain areas that are easier to reach surgically.
- **c.** Unlike other emotions, anxiety depends on only a single neurotransmitter.
- **d.** Researchers can measure anxiety better than other emotions in laboratory animals.

7. After damage to the amygdala, what happens to the startle reflex?

- **a.** It becomes stronger than before.
- **b.** It becomes weaker than before.
- **c.** It disappears altogether.
- **d.** It becomes more consistent from one time or situation to another.

8. The bed nucleus of the stria terminalis is most important for which aspect of anxiety?

- **a.** The sudden increase in anxiety after a signal of danger
- **b.** The general background level of anxiety
- **c.** Inhibiting visible expressions of anxiety
- **d.** Directing attention to signals of danger

9. The amygdala responds most strongly to which type of emotional expressions?

- **a.** Expressions that include both sight and sound
- **b.** Expressions that require some effort to understand
- **c.** Expressions that are directed away from the viewer
- **d.** Expressions of happiness or sadness

10. Three people with amygdala damage expressed no fear under most circumstances. Which of the following did, nevertheless, evoke fear?

- **a.** Standing too close to a stranger
- **b.** Holding a snake
- **c.** Breathing concentrated carbon dioxide
- **d.** Watching a horror movie

11. What neurotransmitter abnormality is most common in people with panic disorder?

- **a.** Decreased glutamate and increased serotonin
- **b.** Decreased norepinephrine and increased oxytocin
- **c.** Decreased GABA and increased orexin
- **d.** Decreased ghrelin and increased leptin

12. What do benzodiazepines do?

- **a.** They decrease cortisol secretion.
- **b.** They increase secretion of orexin.
- **c.** They facilitate GABA synapses.
- **d.** They inhibit serotonin synapses.

Answers: 1a, 2c, 3a, 4c, 5b, 6d, 7d, 8b, 9b, 10c, 11c, 12c.

Module 11.3

Emotional Reactions to Stress

Learning Objectives

After studying this module, you should be able to:

9. Define the general adaptation syndrome.
10. Describe the effects of stress on the nervous system and the immune system.
11. Discuss coping with stress.

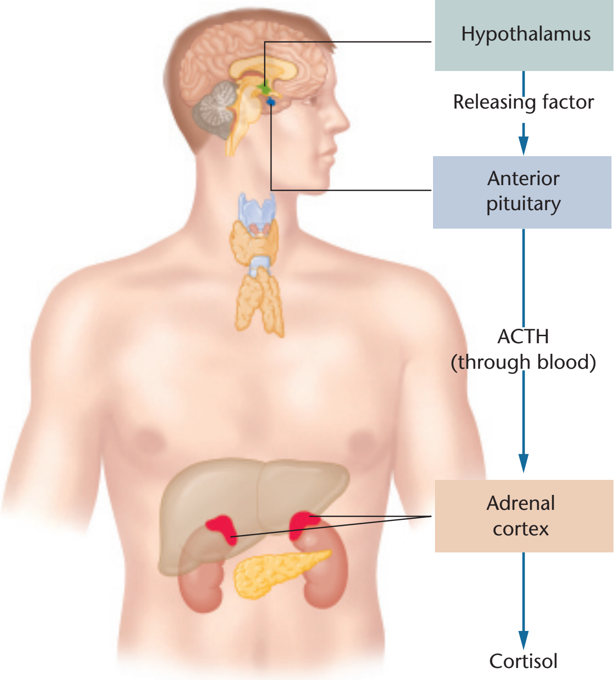
Stress is a major cause of emotion, and emotional reactions to stress are a major factor in disease. In the early days of scientific medicine, physicians made little allowance for the influence of emotions. Today, we accept the idea that emotions and related experiences influence both illness and recovery. **Behavioral medicine** emphasizes the effects of stressful experiences, diet, smoking, exercise, and other behaviors.

Stress and the General Adaptation Syndrome

Hans Selye (1979) popularized the concept of **stress**, defining it as the nonspecific response of the body to any demand made upon it. When Selye was in medical school, he noticed that patients with a wide variety of illnesses have much in common: They develop a fever, they lose their appetite, they become inactive and sleepy most of the day, their sex drive declines, and their immune systems become more active. Later, when doing laboratory research, he found that rats exposed to an injection of anything, as well as heat, cold, pain, confinement, or the sight of a cat responded with increased heart rate, breathing rate, and adrenal secretions. Selye inferred that any threat activated a generalized response, which he called the **general adaptation syndrome**. In the initial stage, which he called *alarm,* the sympathetic nervous system prepares the body for brief emergency activity. Stress also activates the **HPA axis**, consisting of the hypothalamus, pituitary gland, and adrenal cortex (Figure 11.21). The anterior pituitary gland secretes **adrenocorticotropic hormone (ACTH)**, which stimulates the adrenal cortex to secrete glucocorticoid hormones, mainly **cortisol** in humans. Cortisol increases blood glucose, providing the body with extra energy. Cortisol increases alertness and reduces inflammation. The HPA axis reacts to stress more gradually than the sympathetic nervous system, but its effects continue as long as the stress continues.

Figure 11.21 The hypothalamus-pituitary-adrenal cortex axis

Stressful events increase secretion of the adrenal hormone cortisol, which elevates blood sugar, increases metabolism, and enhances alertness.



During the second stage, *resistance,* the adrenal glands continue secreting cortisol and other hormones that maintain alertness and readiness to respond. The body adapts to the prolonged situation by decreasing less-urgent activities, including sexual behavior. After intense, prolonged stress, the body enters the third stage, *exhaustion,* when the nervous and immune systems no longer have the energy to sustain their responses.

Stress-related illnesses and psychiatric problems are widespread in industrial societies, possibly because of changes in the type of stresses we face. In our evolutionary past, the alarm stage readied our ancestors for fight or flight. Today, as Robert Sapolsky (1998) has noted, many of our crises are prolonged, such as working under a domineering boss, paying bills with inadequate income, or caring for a relative with a chronic health problem.

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Selye's concept of stress included any *change* in one's life, including both favorable and unfavorable events. Bruce McEwen (2000, p. 173) proposed an alternative definition that is better for most purposes: "events that are interpreted as threatening to an individual and which elicit physiological and behavioral responses." Although this definition differs from Selye's, both definitions emphasize that the body reacts to many kinds of stress in similar ways. Still, as Jerome Kagan (2016) observed, researchers' concepts of stress have ranged from life-threatening events to matters of brief inconvenience. Consequently, many research studies have reached contradictory conclusions.

Stop & Check

21. What function does cortisol play in the initial response to stress?

22. How does McEwen's definition of stress differ from Selye's?

See page 380 for the answer.

Stress and the Hypothalamus-Pituitary-Adrenal Cortex Axis

Stress can impair health indirectly by altering people's behaviors. Widows and widowers have a greatly increased risk of heart attack or stroke for the next several months (Carey et al., 2014), largely because they tend to eat worse meals, consume more alcohol, sleep less, and exercise less than previously (Fagundes and Wu, 2020). Stress also alters nervous system activity in ways that impair health.

Brief or moderate stress improves energetic performance, vigilance, and memory formation, especially for learning fears (Sapolsky, 2015). However, people under intense stress tend to remember clearly other events that they experienced under stress, and not to remember very well anything that happened in less stressful occasions (Schwabe et al., 2022). (You don't want to be under intense stress while you are taking a test, unless you *studied* while under intense stress.) In a situation that requires problem-solving, highly stressed people tend to fall back onto their habits instead of considering new options (Arnsten, 2015; Girotti et al., 2018).

Brief stress enhances activity of the immune system, helping it fight illnesses, but prolonged stress impairs immune activity and memory (Benschop et al., 1995; Mika et al., 2012). Let's consider the immune system.

The Immune System

The **immune system** consists of cells that protect the body against viruses, bacteria, and other intruders. The immune system is like a police force: If it is too weak, the criminals (viruses and bacteria) run wild and create damage. If it becomes too strong, it might start attacking law-abiding citizens (the body's own cells). When the immune system attacks normal cells, we call the result an *autoimmune disease*. Myasthenia gravis and rheumatoid arthritis are autoimmune diseases.

The primary components of the immune system are the **leukocytes**, commonly known as white blood cells. We distinguish several types of leukocytes, including B cells, T cells, and natural killer cells (Figure 11.22):

- *B cells,* which mature mostly in the bone marrow, secrete **antibodies**, which are Y-shaped proteins that attach to antigens, just as a key fits a lock. Every cell has surface proteins called **antigens** (antibody-generator molecules), and you have your own unique antigens. The B cells recognize "self" antigens, but when they find an unfamiliar antigen, they attack the cell. This kind of attack defends the body against viruses and bacteria, but it also causes rejection of organ transplants from an incompatible donor, unless physicians take special steps to minimize the attack. After the body has made antibodies against a particular intruder, it "remembers" the intruder and quickly builds more of the same kind of antibody if it encounters that intruder again.
- *T cells* mature in the thymus gland. Several kinds of T cells attack intruders directly (without secreting antibodies), and some help other T cells or B cells to multiply.
- *Natural killer cells,* another kind of leukocytes, attack tumor cells and cells that are infected with viruses. Whereas each B or T cell attacks a particular kind of foreign antigen, natural killer cells attack all intruders.

In response to an infection, leukocytes and other cells produce small proteins called **cytokines** (e.g., interleukin-1, or IL-1) that combat infections. Cytokines also stimulate the vagus nerve and trigger the release of **prostaglandins** that cross the blood–brain barrier and stimulate the hypothalamus to produce fever, sleepiness, lack of energy, lack of appetite, and loss of sex drive (Maier and Watkins, 1998; Saper et al., 2012). Cytokines fight the illness, but when cytokine levels get too high, they produce nasal congestion, a runny nose, and other symptoms associated with illness. Recall Selye's observation that most illnesses produce similar symptoms, such as fever, loss of energy, and so forth. Here we see the explanation.

Most people think of fever, sleepiness, and loss of appetite as something the illness did to them, but in fact, they are strategies that evolved for fighting the illness. A moderate fever helps fight many infections. Sleep and inactivity conserve energy so that the body can devote more energy to its immune attack against the intruders (Sinner et al., 2021). Decreased appetite is helpful by decreasing the need for activity, and by reducing blood glucose, the preferred fuel for many microorganisms (Saper et al., 2012).

Stop & Check

23. What kind of cell releases cytokines?

24. What changes do prostaglandins stimulate?

See page 380 for the answer.

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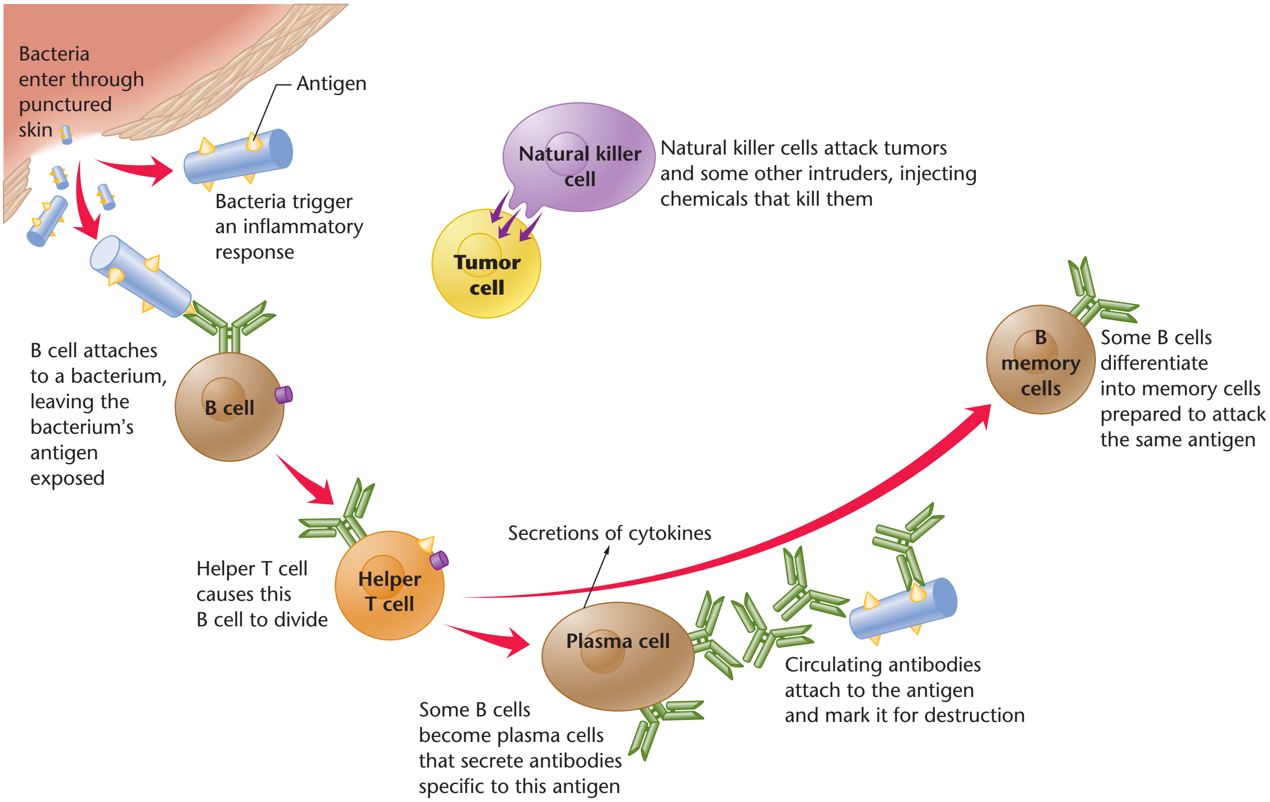
Figure 11.22 Immune system responses to a bacterial infection

B cells bind to bacteria and produce antibodies against the bacteria. When a helper T cell attaches to the B cell, it stimulates the B cell to generate copies of itself, called B memory cells, that immunize the body against future invasions by the same kind of bacteria.


Bacteria enter through punctured skin
Antigen
Bacteria trigger an inflammatory response
Natural killer cell
Tumor cell
Natural killer cells attack tumors and some other intruders, injecting chemicals that kill them
B memory cells
Some B cells differentiate into memory cells prepared to attack the same antigen
B cell attaches to a bacterium, leaving the bacterium's antigen exposed
B cell
Secretions of cytokines
Helper T cell causes this B cell to divide
Helper T cell
Plasma cell
Circulating antibodies attach to the antigen and mark it for destruction
Some B cells become plasma cells that secrete antibodies specific to this antigen

Effects of Stress on the Immune System

The nervous system has more control than we might have guessed over the immune system. The study of this relationship, called **psychoneuroimmunology**, deals with how experiences alter the immune system and how the immune system in turn influences the central nervous system.

In response to a brief stressful experience, the nervous system activates the immune system to produce more natural killer cells and cytokines. The cytokines help combat infections that might result from an injury, and they also trigger prostaglandins that reach the hypothalamus, where they produce the same effects as an illness—sleepiness, decreased appetite, and elevated body temperature (Maier and Watkins, 1998). Even viewing extremely disgusting images can activate the immune system and raise body temperature (Stevenson et al., 2012). In short, if you have been under much stress and start to exhibit symptoms of illness, one possibility is that your symptoms are reactions to the stress, acting through the immune system.

A prolonged stress response produces symptoms of depression and weakens the immune system (Lim et al., 2012; Segerstrom and Miller, 2004). In 1979, a major accident at the Three Mile Island nuclear power plant was barely contained. The people who continued to live near it during the next year had lower than normal levels of B cells, T cells, and natural killer cells. They complained of emotional distress and demonstrated impaired performance on a proofreading task (Baum et al., 1983; McKinnon et al., 1989). A study of research scientists in Antarctica found that a 9-month period of cold, darkness, and social isolation reduced T cell functioning to about half of normal levels (Tingate et al., 1997).

A series of studies have taken measures of people's behaviors and then exposed them (with their permission, of course) to viruses that could cause colds or influenza. People who had been under chronic stress were more likely than average to express symptoms of illness. People who had much social support, physical activity, and adequate sleep were less likely to become ill (Cohen, 2021). Brief or mild levels of stress produces cortisol that puts the brakes on excess cytokines that produce symptoms of illness, but after prolonged stress, the body becomes less responsive to cortisol and the inflammation continues unabated.

Prolonged stress can also harm the hippocampus. Cortisol resulting from stress increases metabolic activity in the hippocampus, making its cells more vulnerable to damage by toxic chemicals or overstimulation (Sapolsky, 1992). Rats exposed to high stress—such as being restrained in a mesh wire retainer for 6 hours a day for 3 weeks—exhibit shrinkage of dendrites in the hippocampus and impairments in the kinds of memory that depend on the hippocampus (Kleen et al., 2006).

The Role of the Enteric Nervous System

When you experience stress, you notice stomach churning, diarrhea, and other signs of digestive upset. These are products of the **enteric nervous system**, a set of neurons that control digestion, stretching from the esophagus to the rectum. The enteric system reacts to stress because of input from the brain and from the hormones released by stress.

Much of the variance in how you respond to stress comes from the bacteria in the digestive system. Most of those bacteria are helpful, but some produce irritable bowel syndrome and visceral pain, and some produce chemicals that increase the risk of anxiety and depression (Carabotti et al., 2015; Needham et al., 2022). Your reaction to stress depends on what happens throughout your body, not just what happens in your brain.

Stop & Check

25. Why do the effects of stress mimic the effects of illness?
26. How does prolonged stress damage the hippocampus?
27. How might antibiotic drugs affect mood?

See page 380 for the answer.

Coping with Stress

People vary in their reactions to a stressful experience because of both genetic predispositions and previous experiences. **Resilience**—the ability to recover well from a traumatic experience—increases with strong social support, an optimistic viewpoint, and reappraisal of difficult situations. Those factors in turn correlate with the ability to rapidly activate the stress response and then rapidly deactivate it (Horn et al., 2016). Successfully coping with moderately stressful events prepares people to cope with later events, and a history of severely adverse events leaves them too exhausted to resist (Seery et al., 2013).

The ways to control stress responses include special breathing routines, exercise, meditation, and distraction, as well as, of course, trying to deal with the problem that caused the stress. Rapid breathing increases alertness and slow breathing promotes calmness (Yackle et al., 2017). Social support is one of the most powerful methods of coping with stress. People who receive more frequent hugs have a lower risk of infection (Cohen et al., 2015). (Yes, try it yourself. Hug somebody.) People who feel rejected have an increased risk (Murphy et al., 2015). In one study, happily married women received moderately painful shocks to their ankles. On various trials, they held the hand of their husband, a man they did not know, or no one. Holding the husband's hand reduced the response indicated by fMRI in several brain areas, including the prefrontal cortex. Holding the hand of an unknown man reduced the response a little, on average, but not as much as holding the husband's hand (Coan et al., 2006). As predicted, the brain responses corresponded to people's self-reports that social support from a loved one helps reduce stress.

Resilience is not easy to investigate. The ideal way is to study many people before and after a stressful experience, keeping track of each person's whereabouts over several years. The organization in the best position to do such a study is the military. Beginning in 2009, the U.S. Army has studied healthy young people entering military service, many of whom experienced serious stress over the next few years. The ones expressing the greatest distress—that is, the least resilience—were those with previous traumas, previous serious concussions, previous mental health issues, and no close social relationships (Ursano et al., 2020; Zuromski et al., 2020).

Module 11.3 | In Closing

Emotions and Body Reactions

Decades ago, Hans Selye argued that any stressful event leads to the general adaptation syndrome, marked by fever and other signs of illness. We now see why: The body reacts to prolonged stress by activating the adrenal cortex and the immune system, and the resulting increase in cytokines produces the same reactions that an infection would. Research has also improved our understanding of the predispositions behind post-traumatic stress disorder. Emotional states, which once seemed too ephemeral for scientific study, are now part of mainstream biology.

Summary

1. Hans Selye introduced the idea of the general adaptation syndrome, which is the way the body responds to any kind of illness or stress. **376**
2. Stress immediately activates the sympathetic nervous system. The hypothalamus-pituitary-adrenal cortex axis responds more slowly but it can persist as long as necessary. The adrenal cortex releases cortisol, which increases metabolism and alertness. **376**
3. Although brief stress enhances the immune response and facilitates memory formation, prolonged stress drains the body of its resources. People under intense stress tend to rely on their habits instead of flexible thinking. **376**
4. Stress activates the immune system, helping to fight viruses and bacteria. The immune system releases cytokines, which stimulate the hypothalamus by releasing prostaglandins, which cross the blood–brain barrier. The hypothalamus reacts by activities to combat illness, including sleepiness, fever, and loss of appetite and energy. **377**
5. Because stress causes release of cytokines, it can also lead to the same symptoms as an illness. **377**
6. The high cortisol levels associated with prolonged stress can damage cells in the hippocampus. **378**
7. People vary in their resilience to stress, based on genetics, social support, and previous experiences. **379**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

adrenocorticotropic hormone (ACTH) **376**
antibodies **377**
antigens **377**
behavioral medicine **376**
cortisol **376**
cytokine **377**
enteric nervous system **379**
general adaptation syndrome **376**
HPA axis **376**
immune system **377**
leukocyte **377**
prostaglandins **377**
psychoneuroimmunology **378**
resilience **379**
stress **376**

Thought Question

If someone were unable to produce cytokines, what would be the consequences?

Stop & Check Answers

21. Cortisol increases blood levels of glucose and therefore makes more energy available. It also increases alertness.
22. Selye's definition treated favorable and unfavorable changes as equally stressful. McEwen's definition focuses on events that an individual considers threatening.
23. Leukocytes (white blood cells) release cytokines.
24. Prostaglandins stimulate the hypothalamus to produce fever, decrease hunger, decrease sex drive, and increase sleepiness.
25. Both release cytokines, which communicate with the hypothalamus via prostaglandins. The hypothalamus reacts with the same responses it uses to combat illness, such as inactivity and loss of appetite.
26. Stress increases the release of cortisol, which enhances metabolic activity throughout the body. When neurons in the hippocampus have high metabolic activity, they become more vulnerable to damage by toxins or overstimulation.
27. If someone has harmful bacteria in the digestive system, antibiotics might improve mood. On the other hand, most people's intestinal bacteria are helpful, and killing them would be a disadvantage.

Module 11.3 | End-of-Module Quiz

1. Under which definition(s), if either, would getting married count as a stressful event?
   - **a.** Selye's definition
   - **b.** McEwen's definition
   - **c.** Both definitions
   - **d.** Neither definition
2. Which gland releases cortisol?
   - **a.** The pituitary gland
   - **b.** The adrenal gland
   - **c.** The pancreas
   - **d.** The thyroid gland
3. What happens to memory when people are under intense stress?
   - **a.** They are unable to form new memories.
   - **b.** They form new memories but rapidly forget them.
   - **c.** They remember mainly useless details.
   - **d.** They remember other stressful events clearly.
4. How does prolonged stress cause fever?
   - **a.** Stressful experiences halt production of leukocytes.
   - **b.** Stress prevents a balance between the sympathetic and parasympathetic nervous systems.

   - **c.** Stress causes an increased number of mitochondria per cell.
   - **d.** Stress elevates cytokines that cause the hypothalamus to increase body temperature.

5. How does stress affect the hippocampus?
   - **a.** Suppression of the immune system breaks down the blood-brain barrier.
   - **b.** Neurons undergo apoptosis because of inadequate stimulation.
   - **c.** Increased metabolic rate makes the hippocampus more vulnerable.
   - **d.** Expansion of surrounding brain areas puts pressure on the hippocampus.

6. Which of these increases resilience?
   - **a.** Unpredictability of events
   - **b.** Social support
   - **c.** Weight gain
   - **d.** Sleep apnea

Answers: 1a, 2b, 3d, 4d, 5c, 6b.

Suggestions for Further Reading

Damasio, A. (1999). *The feeling of what happens.* New York: Harcourt Brace. A neurologist's account of the connection between emotion and consciousness, full of interesting examples.

Frazzetto, G.B. (2013). *Joy, guilt, anger, love.* New York: Penguin books. Insightful description of emotional experiences, with reference to relevant neurological studies.

McEwen, B. S., with Lasley, E. N. (2002). *The end of stress as we know it.* Washington, DC: Joseph Henry Press. Readable review by one of the leading researchers.

Pfaff, D. W. (2007). *The neuroscience of fair play.* New York: Dana Press. Exploration of how the physiology of emotions, especially the amygdala, relates to moral behavior.

Chapter 12

Learning produces amazingly complex behaviors.

(Kali9/E+/Getty Images)

Learning, Memory, and Intelligence

Chapter Outline

Module 12.1
Memory and Memory Loss
Localized Representations of Memory
Types of Memory
Memory Loss
In Closing: Memory and Forgetting

Module 12.2
The Hippocampus and Other Brain Areas
Memory Loss after Damage to the Hippocampus
Navigation
The Striatum
Cortical Areas
In Closing: Brain Damage and Memory

Module 12.3
Cellular Mechanisms of Memory
Blind Alleys and Abandoned Mines
Learning and the Hebbian Synapse
Single-Cell Mechanisms of Invertebrate Behavior Change
Long-Term Potentiation in Vertebrates
Improving Memory
In Closing: The Physiology of Memory

Module 12.4
Intelligence
Genetics and Intelligence
Brain Size and Intelligence
Brain Evolution
In Closing: Why Are We So Intelligent?

Learning Objectives

After studying this chapter, you should be able to:

1. Explain why Lashley's search for the engram of memory failed and why a later attempt succeeded.
2. Distinguish among types of memory.
3. Describe the current view of consolidation of memory.
4. Discuss the biological basis of Alzheimer's disease.
5. Evaluate explanations for infant amnesia.
6. Describe the effects of hippocampal damage on memory.
7. Discuss and evaluate current views of the function of the hippocampus in memory.
8. Describe how the hippocampus and surrounding areas relate to navigation.
9. Contrast the role of the hippocampus to those of the striatum and other areas.
10. Define Hebbian synapses.
11. Explain what we learned about memory from studies of *Aplysia*.
12. Explain the mechanism of long-term potentiation.
13. Evaluate attempted methods of improving memory.

Suppose you type something on your computer and save it. Later, you come back, click the file name, and retrieve what you wrote. How did the computer remember what to do?

That question has two parts: First, how do the physical properties of silicon chips enable them to alter their properties when you type certain keys? Second, how does the wiring diagram take the changes in individual silicon chips and convert them into a useful activity?

Similarly, explaining your memory has two parts: First, how does a pattern of sensory information alter the input–output properties of neurons? Second, after neurons change their properties, how does the nervous system produce useful behavioral changes?

In the first two modules of this chapter, we consider how brain areas interact to produce learning and memory. In the third module, we turn to the mechanisms of how experience changes neurons and synapses. In the final module, we consider the elusive concept of intelligence.

Module 12.1

Memory and Memory Loss

Learning Objectives

After studying this module, you should be able to:

1. Explain why Lashley's search for the engram of memory failed and why a later attempt succeeded.
2. Distinguish among types of memory.
3. Describe the current view of consolidation of memory.
4. Discuss the biological basis of Alzheimer's disease.
5. Evaluate explanations for infant amnesia.

Suppose you lost your ability to form memories. You are aware of the present, but you forget your experience from even a moment ago. You feel as if you just awakened from a deep sleep. You write on a sheet of paper, "Just now, for the first time, I have suddenly become conscious!" A little later, you forget this experience, too. As far as you can tell, you have just now emerged into consciousness after a long sleeplike period. You look at this sheet of paper on which you wrote about becoming conscious, but you don't remember writing it. How odd! You must have written it when in fact you were not conscious! Irritated, you cross off that statement and write anew, "*Now* I am for the first time conscious!" And a minute later, you cross that one off and write it again. Eventually, someone finds this sheet of paper on which you have repeatedly written and crossed out statements about suddenly feeling conscious for the first time.

Sound far-fetched? It really happened to a patient who developed severe memory impairments after encephalitis damaged his temporal cortex (Wilson et al., 1995). Life without memory means no sense of existing across time. Your memory is almost synonymous with your sense of self.

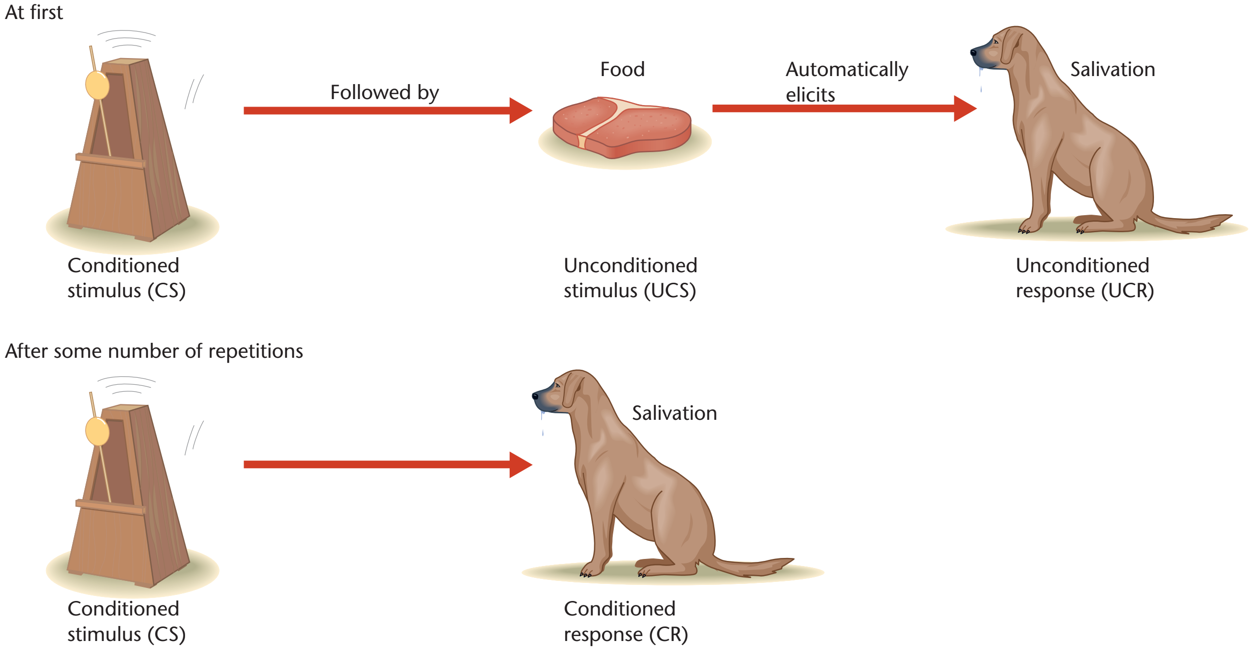
Localized Representations of Memory

Psychologists traditionally distinguish two categories of learning, classical and instrumental conditioning. The Russian physiologist Ivan Pavlov pioneered the investigation of what we now call **classical conditioning** (Figure 12.1a), in which pairing two stimuli changes the response to one of them (Pavlov, 1927). The experimenter presents a **conditioned stimulus (CS)** that initially elicits no response of note, and then presents the **unconditioned stimulus (UCS)** that automatically elicits the **unconditioned response (UCR)**. After some pairings of the CS and the UCS (perhaps just one or two, perhaps many), the individual begins making a new response to the CS, called a **conditioned response (CR)**. In his original experiments, Pavlov presented a dog with a sound (CS) followed by meat (UCS), which stimulated the dog to salivate (UCR). After enough pairings, the sound alone (CS) stimulated the dog to salivate (CR). In that case and many others, the CR resembles the UCR, but in some cases, it does not. For example, if a rat experiences a CS paired with shock, the shock elicits screaming and jumping, but the CS elicits a freezing response.

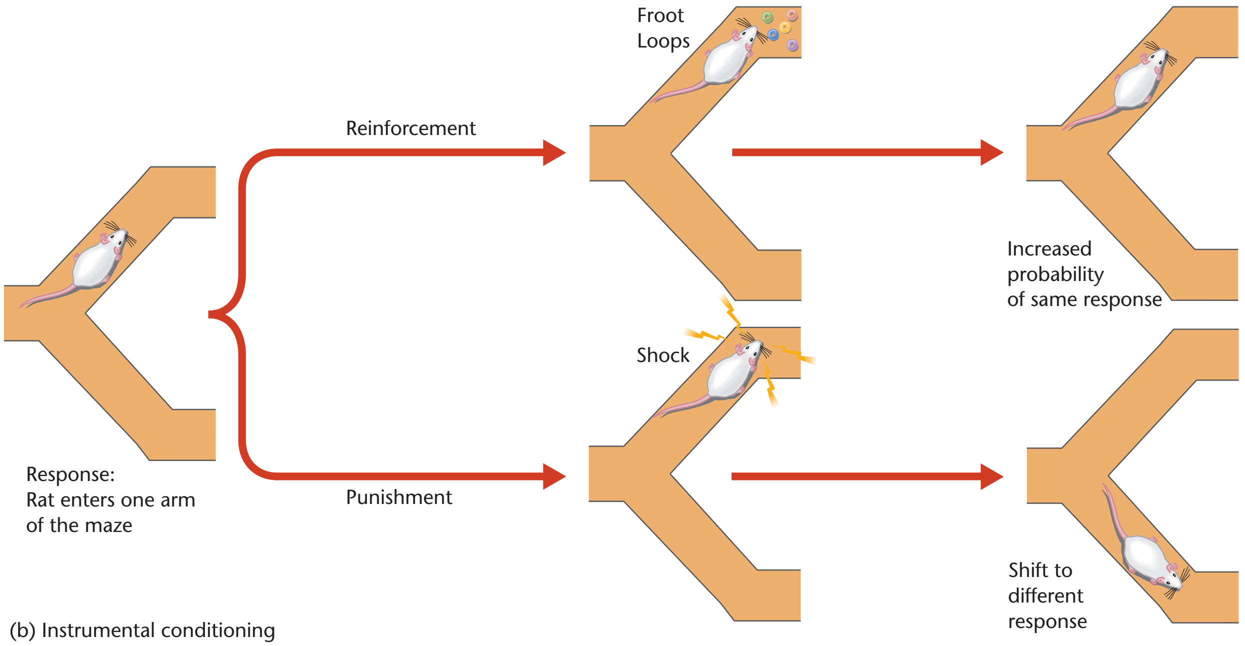
In **instrumental conditioning** (also known as operant conditioning), a response leads to a reinforcer or punishment (Figure 12.1b). A **reinforcer** increases the future probability of the response, and a **punishment** suppresses the frequency. For example, when a rat enters one arm of a maze and finds Froot Loops cereal (a treat that rats seem to love), the rat increases its probability of entering that arm at future opportunities. If it receives a shock instead, the probability decreases. The primary difference between classical and instrumental conditioning is that in instrumental conditioning the individual's response determines the outcome (reinforcer or punishment), whereas in classical conditioning the

Figure 12.1 Classical conditioning and instrumental conditioning

(a) In classical conditioning, two stimuli (CS and UCS) are presented at certain times regardless of what the learner does. **(b)** In instrumental conditioning, the learner's behavior controls the presentation of reinforcer or punishment.


At first
Followed by
Food
Automatically elicits
Salivation
Conditioned stimulus (CS)
Unconditioned stimulus (UCS)
Unconditioned response (UCR)
After some number of repetitions
Salivation
Conditioned stimulus (CS)
Conditioned response (CR)

(a) Classical conditioning


Froot Loops
Reinforcement
Increased probability of same response
Shock
Response: Rat enters one arm of the maze
Punishment
Shift to different response

(b) Instrumental conditioning

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CS and UCS occur at certain times regardless of the individual's behavior. The conditioned response is useful, however, in preparing for the UCS.

Some cases of learning are difficult to label as classical or instrumental. For example, after a male songbird hears the song of his own species during his first few months, he imitates it the following year. The song that he heard was not paired with any other stimulus, so it doesn't look like classical conditioning. He learned the song without reinforcers or punishments, so we cannot call it instrumental conditioning either. Furthermore, learning varies from one situation to another. In most situations, learning occurs only if the CS and UCS, or response and reinforcer, occur close together in time. But if you eat something, especially something unfamiliar, and you get sick later, you learn an aversion to the taste of that food, even if taste and illness are separated by hours (Rozin and Kalat, 1971; Rozin and Schull, 1988).

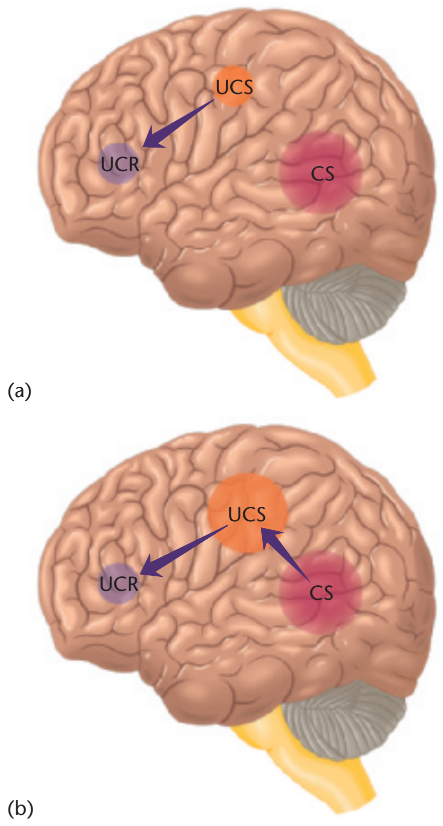
Lashley's Search for the Engram

What happens in the brain when you learn something? Pavlov proposed that classical conditioning reflects a strengthened connection between a CS center and a UCS center in the brain that lets excitation of the CS center flow to the UCS center, evoking a response just like the unconditioned response (Figure 12.2). We now know that this hypothesis does not fit all behavioral observations. If a signal predicts shock, a rat reacts to the signal by freezing, instead of jumping and screaming as if it had received a shock. However, psychologists of an earlier era were unaware of such observations and considered Pavlov's hypothesis plausible. Karl Lashley set out to test it, searching for the **engram**—the physical representation of what has been learned. A connection between two brain areas would be a possible example of an engram.

Lashley reasoned that if learning depends on new or strengthened connections between brain areas, a knife cut somewhere in the brain should interrupt that connection and abolish the learned response. He trained rats on mazes and a brightness discrimination task and then made cuts in their cerebral cortices (Lashley, 1929, 1950) (Figure 12.3). However, no knife cut significantly impaired a rat's performance. Because neither of these tasks is a case of classical conditioning, they were not ideal ways to test Pavlov's theory. Regardless, Lashley's results shared that at least some types of learning did not depend on connections across the cortex.

Figure 12.2 Pavlov's proposal to explain learning

(a) Initially, the UCS excites the UCS center, which excites the UCR center. The CS excites the CS center, which elicits no response of interest. **(b)** After training, excitation in the CS center flows to the UCS center, thus eliciting the same response as the UCS.



Lashley also tested whether any portion of the cerebral cortex is more important than others for learning. He trained rats on mazes before or after he removed portions of the cortex. The lesions impaired performance, but the deficit depended more on the amount of brain damage than on its location. Lashley therefore proposed two principles about the nervous system:

- **equipotentiality**—all parts of the cortex contribute equally to complex behaviors such as learning.
- **mass action**—more cortex is better.

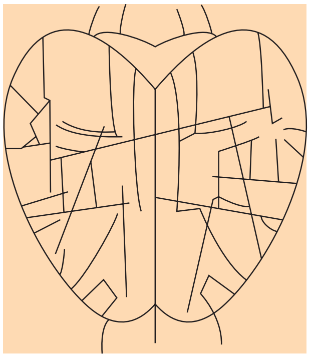
McGraw-Hill Education

Karl S. Lashley (1890–1958)

Psychology is today a more fundamental science than neurophysiology. By this I mean that the latter offers few principles from which we may predict or define the normal organization of behavior, whereas the study of psychological processes furnishes a mass of factual material to which the laws of nervous action in behavior must conform. (Lashley, 1930, p. 24)

Figure 12.3 View of rat brain from above, exhibiting cuts that Lashley made in various rats

No cut or combination of cuts interfered with a rat's memory of a maze.



(**Source:** Adapted from Lashley, 1950)

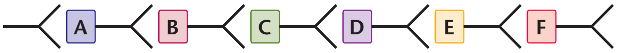
Note, however, another interpretation of Lashley's results: Maze learning and visual discrimination learning are complex tasks in which a rat attends to visual and tactile stimuli, the location of its body, the position of its head, and other cues. Although many brain areas contribute to the learning, they are not necessarily contributing in the same way.

Eventually, researchers found that Lashley's conclusions rested on unnecessary assumptions: (a) that the cerebral cortex is the best or only place to search for an engram and (b) that studying one example of learning is just as good as studying any other one. Investigators who discarded these assumptions reached different conclusions.

The Modern Search for the Engram

Richard F. Thompson and his colleagues used a simpler task than Lashley's and sought the engram in the cerebellum instead of the cerebral cortex. They studied classical conditioning of eyelid responses in rabbits. They presented first a tone (CS) and then a puff of air (UCS) to the cornea of the rabbit's eye. At first, a rabbit closed its eye in response to the air puff but not the tone. After repeated pairings, the tone evoked an eyeblink also. Investigators measured which neurons changed their responses during learning.

Thompson set out to determine the location of learning. Imagine a sequence of brain areas from the sensory receptors to the motor neurons controlling the muscles:



Damaging any of those areas will impair or eliminate the learned response, but we cannot be sure that learning occurred in the damaged area. For example, if the learning occurs in area D, damage in A, B, or C will prevent learning by blocking the input to D. Damage in E or F will prevent learning by blocking the output from D. Thompson and colleagues reasoned as follows: Suppose the learning occurs in D. If so, then D has to be active at the time of the learning, and so do the areas leading up to D (A, B, and C). However, learning should not require areas E and beyond. If area E were temporarily blocked, nothing would relay information to the muscles, so we would see no response, but learning could occur nevertheless, and we could see evidence of it later.

Thompson's research identified one nucleus of the cerebellum, the **lateral interpositus nucleus (LIP),** as essential for learning. At the start of training, those cells exhibited little response to the tone, but as learning proceeded, their responses increased (Thompson, 1986). When the investigators temporarily suppressed that nucleus in an untrained rabbit, either by cooling the nucleus or by injecting a drug into it, and then presented the CSs and UCSs, the rabbit exhibited no responses during the training. Then they waited for the LIP to recover and continued training. At that point, the rabbit learned *at the same speed* as animals that had received no previous training. Evidently, while the LIP was suppressed, the training had no effect.

But does learning actually occur *in* the LIP, or does this area just relay the information to a later area where learning occurs? In the next experiments, investigators temporarily suppressed activity in the red nucleus, a midbrain motor area that receives input from the cerebellum. While the red nucleus was suppressed, the rabbits exhibited no responses during training. However, after the red nucleus had recovered, the rabbits immediately exhibited strong learned responses to the tone (Clark and Lavond, 1993; Krupa et al., 1993). In other words, suppressing the red nucleus temporarily prevented the response but did not prevent learning. Learning did not require activity in the red nucleus or any area after it. Thompson and his colleagues concluded that the learning occurred in the LIP. How did they know that learning didn't depend on some area *before* the LIP? If it did, then suppressing the LIP would not have prevented learning. Figure 12.4 summarizes these experiments. This research made it possible for other researchers to explore the mechanisms in more detail, identifying the cells and neurotransmitters responsible for this example of an engram (Freeman, 2015).

The mechanisms for this type of conditioning are the same in many species, including humans. People with damage to the cerebellum exhibit either no conditioned eyeblinks (Daum et al., 1993) or only weak, inaccurately timed ones (Gerwig et al., 2005). However, they report that they know the stimulus predicts a puff of air to the eyes, and they do exhibit a classically conditioned change in skin conductance (Daum et al., 1993). Damage to the cerebellum impairs a learned response only if the response needs to be made with precise timing (Poulos and Thompson, 2015).

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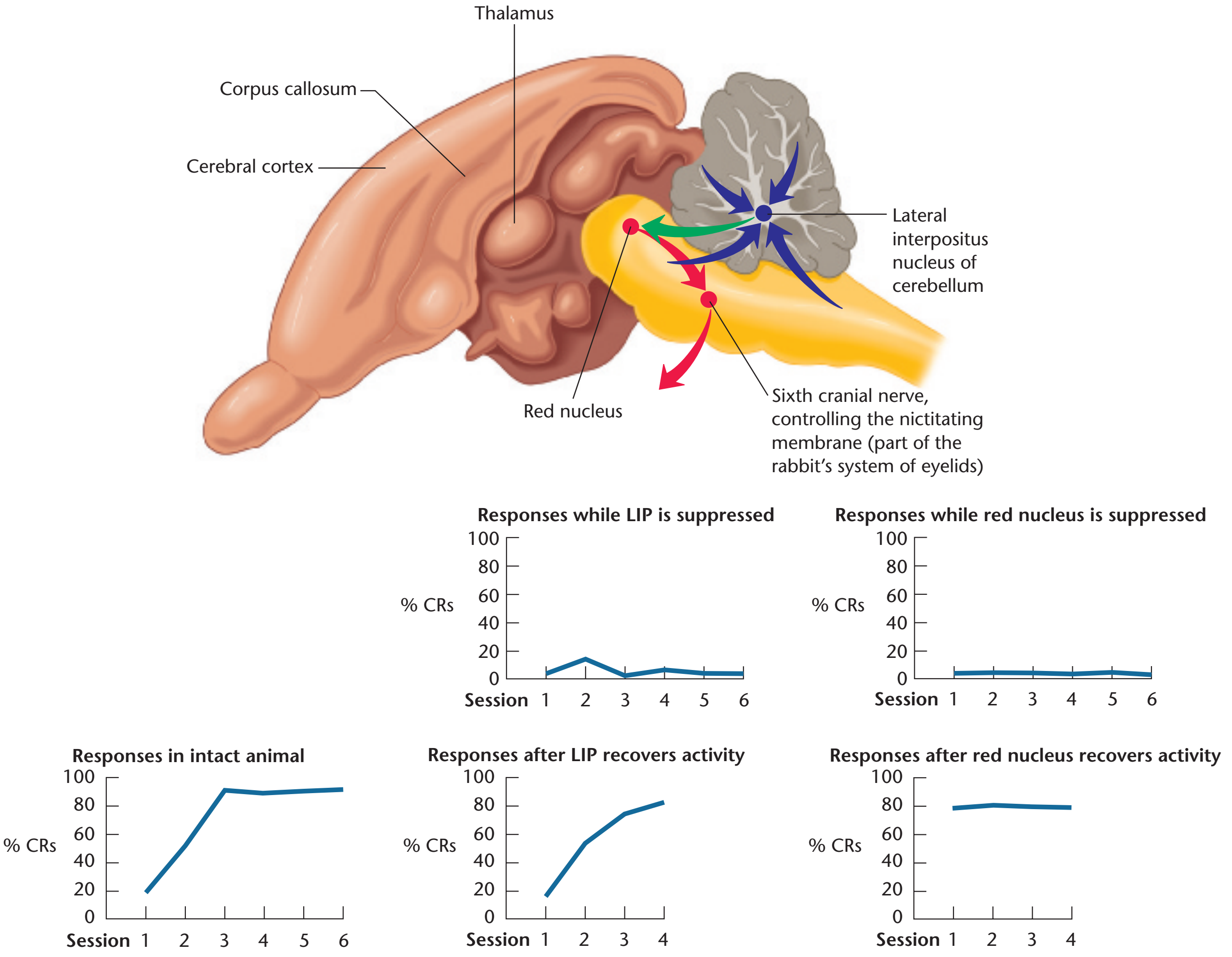
Figure 12.4 Localization of an engram

Temporarily inactivating the lateral interpositus nucleus blocked all indications of learning. After the inactivation wore off, the rabbits learned as slowly as rabbits with no previous training. Temporarily inactivating the red nucleus blocked responses during the period of inactivation, but the learned response appeared as soon as the red nucleus recovered.


Thalamus
Corpus callosum
Cerebral cortex
Lateral interpositus nucleus of cerebellum
Red nucleus
Sixth cranial nerve, controlling the nictitating membrane (part of the rabbit's system of eyelids)
Responses while LIP is suppressed
Responses while red nucleus is suppressed
Responses in intact animal
Responses after LIP recovers activity
Responses after red nucleus recovers activity
% CRs
100
80
60
40
20
0
Session
1
2
3
4
5
6

(**Source:** Based on the results of Clark and Lavond, 1993; Krupa et al., 1993)

Stop & Check

1. Thompson found a localized engram, whereas Lashley did not. What key differences in procedures or assumptions were probably responsible for their different results?
2. What evidence indicated that the red nucleus is necessary for performing the conditioned eyelid response but not for learning it?

See page 393 for the answer.

Types of Memory

Finding an engram for certain types of classical conditioning is an important accomplishment, but finding an engram for everyday memories is more challenging. For much of the 20th century, most psychologists assumed that all memory was the same. If so, they could study it with any convenient example, such as memorizing nonsense syllables, just as physicists can measure gravity by dropping any convenient object. Eventually, psychologists recognized differences among types of memory.

Short-Term and Long-Term Memory

Donald Hebb (1949) reasoned that no one mechanism could account for all the phenomena of learning. You can repeat something you just heard, and you can also describe something you experienced years ago. Hebb could not imagine a physical or chemical process that is fast enough to account for immediate memory yet stable enough for permanent memory. He therefore proposed a distinction

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between **short-term memory** of events that have just occurred and **long-term memory** of events from further back. Several types of evidence supported this idea:

- Short-term memory and long-term memory differ in their capacity. If you hear a series of unrelated numbers or letters, such as DZLAUV, you can probably repeat no more than about seven of them, and with some kinds of material, your maximum is even less. You can hold a vast amount of information in long-term memory.
- Short-term memory requires rehearsal. If you read the letter sequence DZLAUV and then something distracts you, your chance of repeating the letters declines rapidly (Peterson and Peterson, 1959). You can reconstruct long-term memories that you haven't thought about in years.
- Once you have forgotten something from short-term memory, it is lost. With long-term memory, a hint might help you reconstruct something you thought you had forgotten. Try naming all your high school teachers. After you have named as many as you can, you can name still more if someone shares photos with you.

Hebb suggested that we might store short-term memories by a reverberating circuit, in which neuron A excites neuron B, which excites neuron C, which then reexcites neuron A. Hebb further proposed that storing something in short-term memory long enough made it possible for the brain to **consolidate** (strengthen) it into long-term memory, presumably by building new synapses or other structural changes. If anything interrupted the rehearsal of short-term memory before consolidation completed its course, the information was simply lost.

Our Changing Views of Consolidation

Later studies made the distinction between short-term and long-term memory problematic. First, many short-term memories are not simply on their way to being long-term memories. When you watch a soccer or hockey match, you remember the score until it changes. If you park your car, your memory of its location is neither a short-term memory that fades within seconds, nor a memory that will last for years.

Furthermore, consolidation isn't what we used to think it was. The original idea was that the brain held something in short-term memory until it could synthesize new proteins to establish a long-term memory. By that assumption, we should expect that consolidating a memory requires holding it in short-term memory for some fixed amount of time, presumably about the same in all cases. However, the time needed to form a long-term memory varies enormously. To memorize facts that you consider boring and useless, you might struggle for hours. But if someone warns you about the venomous snake that got loose in your dormitory, you won't have to repeat it over and over or write flash cards to remember it. In fact, if an event is extremely arousing—your first kiss, perhaps, or the moment when you heard about some tragedy—you remember not only the event itself but also those just before and after it. Psychologists call these experiences "flashbulb memories," as if a mental flashbulb illuminated everything for a moment. The physiological explanation is that highly emotional experiences arouse the locus coeruleus, which increases norepinephrine release throughout the cortex and dopamine release in the hippocampus (Takeuchi et al., 2016). Emotional experiences also increase the secretion of epinephrine and cortisol that activate the amygdala and hippocampus (Cahill and McGaugh, 1998; Murty et al., 2012). All those changes strengthen the memories forming at the time.

Flashbulb memories have a further aspect: Suppose you are driving on snow and you skid on a slippery patch. Ordinarily, you would forget this minor scare quickly. However, a minute later you skid on a second slippery patch and wreck your car. Now you form a long-term memory of not only the accident but also the earlier slip. Researchers call this the "synaptic tag-and-capture" process: Your brain tags a weak new memory for later stabilization if a similar, more important event soon follows it (Dunsmoor et al., 2015). Your brain also has mechanisms to prevent you from linking events that happen too far apart, such as the next day (Shen et al., 2022).

Working Memory

To improve the concept of short-term memory, A. D. Baddeley and G. J. Hitch (1994) introduced the term **working memory** to refer to the way we store information while we are working with it. One way to test working memory is the **delayed response task**, in which you respond to something that you saw or heard a short while ago. Imagine that while you stare at a central fixation point, a light flashes briefly near the periphery. You continue staring at the central point until you hear a beep, and then you are supposed to look to where you remember seeing the light. Ordinarily, the brain's representation of a visual image decays quickly, but if you need to remember the stimulus to respond to it later, activity in the visual cortex persists (Teeuwen et al., 2021). This task can be modified for use with monkeys and other species. During the delay, cells in the prefrontal and parietal cortex increase their activity, and different cells become active depending on the direction the eye movement will need to take (Chafee and Goldman-Rakic, 1998; Constantinidis and Klingberg, 2016).

During any type of working memory task, a reverberating circuit holds the information, as Hebb had surmised. The information reverberates among neighboring cells in the cortex (Daie et al., 2021) and between the cerebral cortex and the thalamus (Bolkan et al., 2017; Guo et al., 2017; Schmitt et al., 2017). However, cells holding an item in working memory do not simply repeat the stimulus. If you were trying to remember something you had just seen and your visual cortex kept activating the same cells in the same way, that pattern would interfere with seeing anything new. Instead, your visual system codes a simplified account of just the information you need to use. If you saw a series of moving dots and you need to remember which direction most of the dots were moving, your brain would store a representation of that direction, not a copy of all the dots (Kwak and Curtis, 2022).

Stop & Check

3. Why should we conclude that consolidation depends on more than just holding a short-term memory long enough for protein synthesis?
4. What mechanism causes flashbulb memories?
5. How does the cortex store a working memory during a delay?

See page 393 for the answer.

Memory Loss

In many cases, forgetting is a "feature," not a "bug" (Nørby, 2015; Popov et al., 2019). We have genes that suppress consolidation or increase forgetting under various conditions (Noyes et al., 2021). Why would we have evolved genes to increase forgetting? One likely hypothesis is that we need to forget outdated information to replace it with new information. You want to remember where you are supposed to go at 11 o'clock tomorrow morning, and you don't want to confuse that information with your appointment at 9 o'clock three weeks ago. Another hypothesis is that forgetting the details of an event helps you focus on the important general principles.

However, although some forgetting is good, you do not want to forget important or current information. **Amnesia** is memory loss. One patient ate lunch and, 20 minutes later, ate a second lunch, apparently having forgotten the first meal. Another 20 minutes later, he started on a third lunch and ate most of it. A few minutes later, he said he would like to "go for a walk and get a good meal" (Rozin et al., 1998). Other patients with amnesia also forget that they have just eaten, although when they start to eat again, they remark on not enjoying the food as much as usual (Higgs et al., 2008).

One cause of amnesia is "brain fog" that many patients suffer for months after recovery from COVID-19 or from cancer treatments. Brain fog is marked by periods of forgetfulness, confusion, slow thinking, and impaired concentration. One hypothesis for brain fog is that the COVID virus causes a powerful reaction by the immune system that produces enough inflammatory cytokines to damage the blood-brain barrier and activate microglia cells that damage neurons and axons (Fernández-Castañeda et al., 2022). Another hypothesis is that the reaction to the virus impairs the blood flow to the brain (Asadi-Pooya et al., 2022; Theoharides et al., 2021). Many people who recovered from COVID or cancer treatments have a shrinkage of gray matter in parts of the cerebral cortex and decreased levels of myelin (Douaud et al., 2022; Fernández-Castañeda et al., 2022).

Sometimes amnesia is limited to a certain aspect of memory. Two patients with damage in the occipital cortex lost the ability to form new visual memories, such as the ability to recognize something seen a few moments ago, despite satisfactory memory in other ways (Ross, 2019). Two other patients could answer questions like, "Is a library quiet?" but not a question like, "Which is quiet, a concert or a library?" By the time they got to the end of the question, they had forgotten the first part (Martin, 2019).

Here we briefly consider Alzheimer's disease and the phenomenon of infant amnesia. The second module considers amnesia resulting from damage to the hippocampus.

Alzheimer's Disease

The most common cause of severe memory loss is **Alzheimer's** (AHLTZ-hime-ers) **disease**. Daniel Schacter (1983) reported playing golf with an Alzheimer's patient who remembered the rules and jargon of the game correctly but kept forgetting how many strokes he took. Five times he teed off, waited for the other player to tee off, and then teed off again, having forgotten his first shot. Patients with Alzheimer's learn procedural skills better than facts. Sometimes they surprise themselves with their skilled performance because they don't remember doing it before (Gabrieli et al., 1993). Alzheimer's disease gradually progresses to confusion, depression, apathy, hallucinations, delusions, sleeplessness, and loss of appetite. It becomes more common with age, affecting almost half of people over 85 (Evans et al., 1989). The disease is marked by progressive loss of brain cells, as in Figure 12.5.

The first major clue to the cause of Alzheimer's was the observation that most people with *Down syndrome* get Alzheimer's disease if they survive into middle age (Lott, 1982). People with Down syndrome have three copies of chromosome 21 rather than the usual two. That fact led investigators to examine chromosome 21, where they found a gene known as ***APOE***. This gene makes a protein that contributes to many functions, including lipid metabolism and control of the blood-brain barrier. The gene comes in several forms. People with one copy of the type 4 gene (*APOE4*) have four times the normal risk of Alzheimer's, and people with two copies have 15 times the normal risk (Ishii and Iadecola, 2020). Even if people with *APOE4* do not develop Alzheimer's, they are likely to exhibit cognitive decline in old age (Martens et al., 2022).

The *APOE4* gene and at least two other genes are linked to many cases of early-onset Alzheimer's disease (Goate et al., 1991; Murrell et al., 1991). "Early" means before age 60. Heritability is high for early-onset Alzheimer's and somewhat less for the more common late-onset variety. More than 50 genetic loci have been linked to late-onset Alzheimer's. Each of them by itself has only a small contribution, but an examination of all the chromosomes combined can predict the risk of the disease, with accuracy of 80 percent or more (Sims et al., 2020). In addition to genetics, sleep deprivation, excessive salt intake, and lack of exercise increase the risk (Faraco et al., 2018; Holth et al., 2019). Type 2 diabetes is also a major risk factor, because insulin activity in the brain is important for storing memories (De Felice et al., 2022).

Alzheimer's disease is linked to an increase of two brain chemicals, **β-amyloid** and **tau protein** (Montagne et al., 2020;

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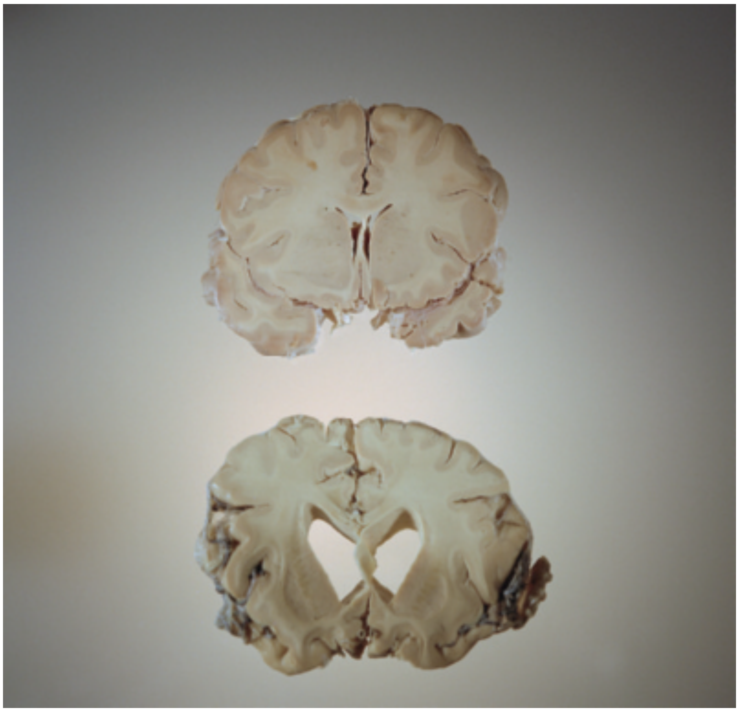
Figure 12.5 Brain atrophy in Alzheimer's disease

A patient with Alzheimer's **(bottom)** has gyri that are shrunken in comparison with those of a person who does not have Alzheimer's **(top)**.



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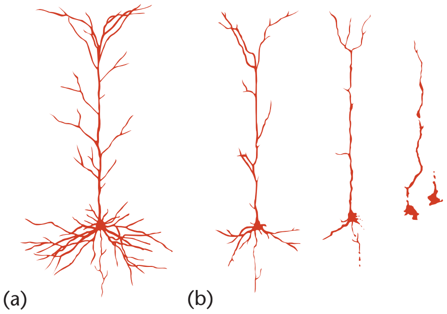
(**Source:** Dr. Robert D. Terry, Department of Neurosciences, School of Medicine, University of California at San Diego.)

Shi et al., 2017, 2021). As amyloid-β and tau accumulate in neurons, they spread within cells and from cell to cell, disrupting neurotransmission, damaging mitochondria, and triggering waves of microglia that kill neurons (Riek and Eisenberg, 2016). They also damage axons and dendrites, causing them to cluster into structures called *plaques*, as Figures 12.6 and 12.7 show (Scheibel, 1983; Selkoe, 2000).

The function of β-amyloid is uncertain. Many old people have high levels of β-amyloid without Alzheimer's disease, and some have Alzheimer's disease without especially high levels of β-amyloid (Herrup, 2015). Although most scientists believe it is one of the causes of Alzheimer's, a minority opinion is that a small amount of β-amyloid might be the brain's effort to protect itself (Hussein, 2021).

Figure 12.6 Neuronal degeneration in Alzheimer's disease

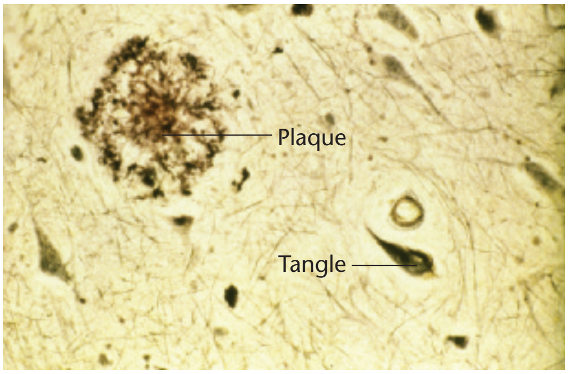
(a) A cell in the prefrontal cortex of a non-Alzheimer's human; **(b)** cells from the same area of cortex in patients with Alzheimer's disease at various stages of deterioration.



(**Source:** Based on "Dendritic changes," by A. B. Scheibel, p. 70. In *Alzheimer's disease,* B. Reisberg, ed., 1983. Free Press.)

Figure 12.7 Cerebral cortex of a patient with Alzheimer's

Plaques and tangles result from β-amyloid and abnormal tau protein.



Dr. M. Goedert/Science Photo Library/Science Source

(**Source:** From Taylor et al., 2002)

Pharmaceutical companies have made many attempts to alleviate Alzheimer's by drugs that counteract β-amyloid, without much success. In 2021, the U.S. Food and Drug Administration granted conditional approval for a new drug to remove β-amyloid as a treatment of Alzheimer's. Many scientists have expressed reservations because the benefits of the drug are uncertain, the side effects are serious, and the cost is high. An important limitation is that Alzheimer's relates to high levels of both β-amyloid and tau, so attacking just β-amyloid is not enough (Busche et al., 2019). The areas of cell damage in the brain correlate better with tau levels than with β-amyloid levels (Musiek and Holtzman, 2015). Tau is principally responsible for *tangles*, structures formed from degeneration within neurons (Figure 12.7). Another explanation for the ineffectiveness of drugs so far is that the damage associated with Alzheimer's may already be too extensive by the time the condition is diagnosed (Canter et al., 2016). An important research goal is to find ways to diagnose Alzheimer's more quickly.

Infant Amnesia

Infant amnesia (or early childhood amnesia) is not a disorder. It is the universal experience that older children and adults remember little of what happened in their first few years. We keep the skills that we learned then, but we forget most or all the episodic memories. Sigmund Freud may have been the first to call attention to this phenomenon. His explanation was that children repress their early memories because of their association with severe sexual conflicts. Few today take that idea seriously. Later psychologists have offered explanations of why young children fail to form long-term memories, but in fact young children do form long-term memories. Three- and four-year-olds, and even some two-year-olds, can accurately describe their last birthday party, their last visit to Grandma's house, or other events from months ago (Peterson et al., 2011; Solter, 2008). Freud was at least asking the right question: Why do we *forget* the memories from early childhood?

Hypotheses have included the development of language, or a sense of self, or complex reasoning abilities as children grow older. However, infant amnesia can be demonstrated in rats and many other species (Madsen and Kim, 2016). Rats in their first weeks of life learn and retain their learning for a day or more, but they soon forget (Brown and Freeman, 2016).

What could explain the difficulty of recalling infant memories? Part of the explanation is that infants do not store memories as well as they can when older (Donato et al., 2021; Tsai et al., 2019). Research with mice points to an additional explanation. Early in life, for mice as for humans, the hippocampus rapidly forms new neurons and replaces old ones with new ones. The formation of new neurons facilitates new learning, but as new neurons and synapses displace old ones, the new learning weakens the old memories.

In contrast to mice and humans, guinea pigs are relatively mature at birth, already walking around and eating solid food. They do not have rapid formation of new hippocampal neurons, and they do not tend to forget their early memories the way rats and humans do. Furthermore, chemical procedures that interfere with formation of new neurons impair both learning and forgetting in infant mice (Akers et al., 2014). Even later in life, procedures that increase the formation of new neurons in the hippocampus have been demonstrated to increase rats' forgetting (Scott et al., 2021). Although we should be cautious about assuming that the mechanisms in rodents are the same as in humans (Epp et al., 2016), a plausible explanation for infant amnesia is that the rapid learning in early childhood displaces memories formed in infancy.

Stop & Check

6. Why did researchers look for a gene on chromosome 21 as a probable cause of early-onset Alzheimer's disease?
7. Which gene, and what chemicals, are most strongly linked to Alzheimer's disease?
8. What are the consequences of rapid formation of new neurons in an infant hippocampus?

See page 393 for the answer.

Module 12.1 | In Closing

Memory and Forgetting

Decades ago, Karl Lashley supposed that the physiology of learning might be a simple matter of increasing a single pathway in the cortex. Today, we distinguish among several types of learning and memory that rely on multiple mechanisms and multiple brain areas. We learn about these mechanisms by studying forgetting as well as by studying learning.

Summary

1. Ivan Pavlov suggested that learning depends on the growth of a connection between two brain areas. Karl Lashley showed that learning does *not* depend on new connections across the cerebral cortex. **384**

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2. Richard Thompson found that certain instances of classical conditioning take place in part of the cerebellum. **387**
3. Psychologists distinguish between short-term memory and long-term memory. Short-term memory holds only a small amount of information and retains it only briefly unless it is constantly rehearsed. **388**
4. Memories consolidate, but not just as a function of time. Memories can consolidate rapidly, slowly, or not at all. **389**
5. "Flashbulb memories" form strongly because of emotional arousal fed to the cortex from the locus coeruleus and other sites. **389**
6. Working memory, a modern alternative to the concept of short-term memory, stores information that one is currently using. The brain maintains a working memory by activity reverberating among cortical cells and between the cortex and the thalamus. The representation holds the information needed for a response, not a complete copy of the sensory information. **389**
7. Alzheimer's disease is a progressive disease characterized by impaired memory and attention. Early-onset Alzheimer's disease has high heritability, with many cases related to the *APOE4* gene. Late-onset Alzheimer's relates to many genes and several environmental influences. **390**
8. Alzheimer's disease is related to accumulation of β-amyloid and tau protein in the brain. **390**
9. Humans as well as many other species exhibit infant amnesia, the loss of most early memories. Early memories are unstable because of an immature hippocampus and because rapid new learning and new neurons in the hippocampus displace older memories. **392**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

Alzheimer's disease **390**
Amnesia **390**
β-amyloid **390**
APOE **390**
classical conditioning **384**
conditioned response (CR) **384**
conditioned stimulus (CS) **384**
consolidate **389**
delayed response task **389**
engram **386**
equipotentiality **386**
infant amnesia **392**
instrumental conditioning **384**
lateral interpositus nucleus (LIP) **387**
long-term memory **389**
mass action **386**
punishment **384**
reinforcer **384**
short-term memory **389**
tau protein **390**
unconditioned response (UCR) **384**
unconditioned stimulus (UCS) **384**
working memory **389**

Thought Question

Lashley sought to find the engram, the physiological representation of learning. In general terms, how would you recognize an engram if you saw one? That is, what would someone have to demonstrate before you could conclude that a particular change in the nervous system was really an engram?

Stop & Check Answers

1. Thompson studied a different type of learning. Also, he looked in the cerebellum instead of the cerebral cortex.
2. When the red nucleus was inactivated during training, the animal made no conditioned responses, so the red nucleus is necessary for the response. However, as soon as the red nucleus recovered, the animal exhibited conditioned responses, so learning occurred while the red nucleus was inactivated.
3. People can store some memories for hours or days without forming a permanent memory, whereas they form emotionally important memories quickly.
4. Emotionally exciting memories stimulate the locus coeruleus, which increases norepinephrine throughout the cortex and dopamine to the hippocampus. Emotional excitement also increases epinephrine and cortisol, which activate the amygdala and hippocampus.
5. Activity reverberates among cortical cells and between the cortex and the thalamus, maintaining a simplified code of just the information needed for a response.
6. Most people with Down syndrome, caused by an extra copy of chromosome 21, develop Alzheimer's disease in middle age.
7. The *APOE4* gene increases the risk of Alzheimer's disease. Two brain chemicals accumulate in this disease: β-amyloid and tau protein.
8. Rapid formation of new neurons in the infant hippocampus facilitates new learning, but at the cost of also increasing forgetting.

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Module 12.1 | End-of-Module Quiz

1. What evidence led Lashley to draw his conclusions of equipotentiality and mass action?

- **a.** Impairing any neurotransmitter produced the same impairment as any other neurotransmitter.
- **b.** Electrical stimulation of the brain could produce either reward or punishment.
- **c.** EEG studies exhibited equal activation throughout the brain during learning.
- **d.** Impairment of learning depended on the amount of damage rather than the location.

2. Which of Lashley's assumptions did later researchers reject?

- **a.** Any convenient example of learning reveals the mechanisms of all learning.
- **b.** Learning requires modification of the activity at synapses.
- **c.** All memories have to consolidate, but some consolidate faster than others.
- **d.** The mechanisms of learning are similar across mammalian species.

3. Why did Thompson conclude that eyeblink conditioning did not depend on the red nucleus?

- **a.** Rabbits learned from training that occurred while the red nucleus was suppressed.
- **b.** The red nucleus did not change its responses after learning.
- **c.** If training occurred while the red nucleus was suppressed, the rabbit had to start over on learning.
- **d.** Inactivating the red nucleus did not interrupt the responses.

4. Why did Hebb infer a difference between short-term and long-term memory?

- **a.** Some memories form quickly and some are permanent.
- **b.** Some memories depend on the hippocampus and some do not.
- **c.** Some memories affect motor behaviors and some do not.
- **d.** Some memories are conscious and some are not.

5. How does emotional arousal facilitate consolidation?

- **a.** Suppression of the production of new neurons in the hippocampus
- **b.** Occasional bursts of gamma oscillations
- **c.** Increased production of amyloid-β
- **d.** Increased release of norepinephrine, epinephrine, and cortisol

6. How does the cortex store a working memory?

- **a.** Suppression of the production of new neurons in the hippocampus
- **b.** Reverberating activity between the thalamus and the cortex
- **c.** Increased production of amyloid-β
- **d.** Increased release of norepinephrine, epinephrine, and cortisol

7. People with which condition are most likely to develop Alzheimer's disease in middle age?

- **a.** Congenital adrenal hyperplasia
- **b.** Down syndrome
- **c.** Williams syndrome
- **d.** Korsakoff syndrome

8. What is known about the heritability of Alzheimer's disease?

- **a.** Early-onset Alzheimer's disease has higher heritability than the late-onset variety.
- **b.** The FTO gene causes many cases of early-onset Alzheimer's disease.
- **c.** Alzheimer's disease results from a combination of two recessive genes.
- **d.** Alzheimer's disease is caused by diet, not by genes.

9. Currently, what seems the most promising explanation for infant amnesia?

- **a.** As children grow older, they repress their painful early sexual conflicts.
- **b.** Forming many new memories in infants replaces old ones.
- **c.** Infants are unable to store a long-term memory.
- **d.** Gamma oscillations fail to form in the infant cortex.

Answers: 1d, 2a, 3a, 4a, 5d, 6b, 7b, 8a, 9b.

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Module 12.2

The Hippocampus and Other Brain Areas

Learning Objectives

After studying this module, you should be able to:

6. Describe the effects of hippocampal damage on memory.
7. Discuss and evaluate current views of the function of the hippocampus in memory.
8. Describe how the hippocampus and surrounding areas relate to navigation.
9. Contrast the role of the hippocampus to those of the striatum and other areas.

People who suffered memory problems after localized brain damage have told us much about memory, especially about the distinctions between one type of memory and another. In this module we concentrate on brain areas with contrasting functions in memory, the hippocampus and the striatum.

Memory Loss after Damage to the Hippocampus

In 1953, Henry Molaison, known in research reports as H. M., was suffering about 10 minor epileptic seizures per day and a major seizure about once a week, despite trying every available antiepileptic drug. Eventually, he agreed to a desperate measure. A surgeon, William Scoville, who had experimented with various forms of lobotomy for mental illness, was familiar with two cases in which removal of much of the medial temporal lobe had relieved epilepsy. Hoping that the same might work with H. M., Scoville removed the hippocampus and nearby structures of the medial temporal cortex from both of H. M.'s hemispheres. Researchers knew almost nothing about the hippocampus at the time, and no one knew what to expect after the surgery. It was a risky procedure, and most of Scoville's colleagues would have advised against it. Although the operation reduced H. M.'s epilepsy to no more than two major seizures per year, he suffered severe memory impairment (Milner, 1959; Penfield and Milner, 1958; Scoville and Milner, 1957). Figure 12.8 compares the normal anatomy of the hippocampus and the damage in H. M.

Anterograde and Retrograde Amnesia

After the surgery, H. M.'s intellect and language abilities remained intact, and his personality remained the same except for emotional placidity (Eichenbaum, 2002). However, he suffered massive **anterograde amnesia** (inability to form memories for events that happened after brain damage). Initially, researchers said his **retrograde amnesia** (loss of memory for events before the brain damage) was confined to the previous 1 to 3 years. Later, they found it was more extensive. H. M. is representative of other people who have suffered amnesia after damage to the hippocampus and surrounding structures of the medial temporal lobe. All exhibit both anterograde and retrograde amnesia, with the retrograde amnesia especially severe for the time leading up to the damage. Most can tell where they lived as a child and as a teenager, but not where they lived 3 years ago (Bayley et al., 2006).

Intact Working Memory

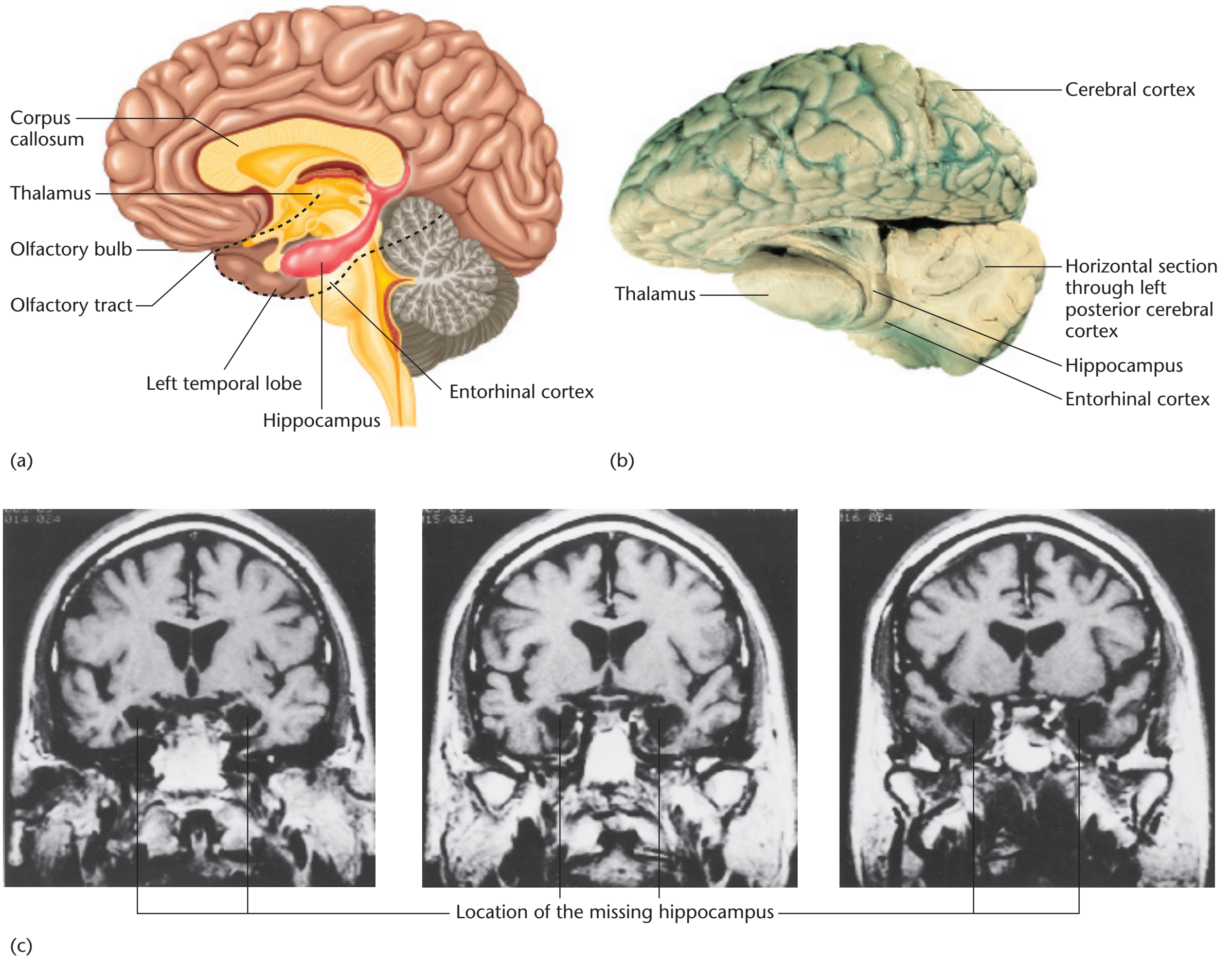
Despite H. M.'s huge deficits in forming long-term memories, his short-term or working memory remained intact, unless he was distracted. Brenda Milner (1959) asked him to remember the number 584. After a 15-minute delay, he recalled it correctly, explaining, "It's easy. You just remember 8. You see, 5, 8, and 4 add to 17. You remember 8, subtract it from 17, and it leaves 9. Divide 9 in half and you get 5 and 4, and there you are, 584. Easy." A moment later, after his attention had shifted to another subject, he had forgotten both the number and the complicated line of thought he had associated with it.

Impaired Storage of Long-Term Memory

Although H. M. could recall much information that he had learned before his damage, he was severely impaired in forming new long-term memories. For several years after his operation, whenever he was asked his age and the date, he answered "27" and "1953." After a few years, he started guessing wildly, generally underestimating his age by 10 years or more and missing the date by up to 43 years (Corkin, 1984). He could read the same magazine repeatedly or work the same jigsaw puzzle repeatedly without losing interest. He

Figure 12.8 The hippocampus and its loss

(a) Location of the hippocampus in the interior of the temporal lobe. The left hippocampus is closer to the viewer than the rest of this plane; the right hippocampus is behind the plane. The dashed line marks the location of the temporal lobe, which is not visible in the midline. **(b)** Photo of a human brain from above. The top part of the left hemisphere has been cut away to show how the hippocampus loops over (dorsal to) the thalamus, posterior to it, and then below (ventral to) it. **(c)** MRI scan of H. M.'s brain, exhibiting absence of most of the hippocampus, plus much of some surrounding structures. The three views exhibit coronal planes at successive locations, anterior to posterior.


Corpus callosum
Thalamus
Olfactory bulb
Olfactory tract
Left temporal lobe
Hippocampus
Entorhinal cortex
(a)
Cerebral cortex
Horizontal section through left posterior cerebral cortex
Thalamus
Hippocampus
Entorhinal cortex
(b)
Location of the missing hippocampus
(c)

could never remember that his favorite uncle had died (Corkin, 2013). Often, he told someone about a childhood incident and then, a minute or two later, told that person the same story again (Eichenbaum, 2002). In 1980, he moved to a nursing home. Four years later, he could not say where he lived or who cared for him. Although he watched the news on television every night, he could recall only a few fragments of events since 1953. He failed to learn the meanings of new words that entered the English language, such as *Jacuzzi* and *granola* (Corkin, 2002).

You might wonder whether he knew his own appearance. Yes and no. When asked whether his hair had turned gray, he replied that he did not know. When shown a photo of himself with his mother, taken long after his surgery, he recognized his mother but not himself. However, when he saw himself in the mirror, he showed no surprise (Corkin, 2002). He had seen himself daily in the mirror over all these years. He also had the context of knowing that the person in the mirror must be himself, whereas the person in the photo could be anyone.

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H. M. gained a few weak **semantic memories**—that is, memories of factual information (Corkin, 2002; O'Kane et al., 2004). For example, when he was given first names and asked to fill in appropriate last names, his replies included some who became famous after 1953, such as these:

	H. M.'s Answer
Elvis	Presley
Martin Luther	King
Billy	Graham
Fidel	Castro
Lyndon	Johnson

He provided even more names when he was given additional information:

	H. M.'s Answer
Famous artist, born in Spain . . .	Pablo Picasso

One study found an interesting qualification to the usual rule that patients with amnesia cannot learn new information. The investigators showed a series of shapes with unrelated labels. Despite many repetitions, patients with amnesia made no progress toward learning the label for each shape. Then the researchers let the patients devise their own labels. The patients had to look at each shape and describe it so that another person, who was looking at the 12 shapes, would know which one the patient was looking at. At first, the descriptions were slow and uninformative. For one shape, a patient said, "The next one looks almost . . . the opposite of somebody kind uh . . . slumped down, on the ground, with the same type of . . ." Eventually, he said it looked like someone sleeping with his knees bent. By the fourth trial, he quickly labeled that shape as "the siesta guy," and he continued saying the same thing from then on, even in later sessions on later days (Duff et al., 2006).

Severe Impairment of Episodic Memory

H. M. had severe loss of **episodic memory** (memory of personal events) in contrast to semantic memory (memory of facts, like what you learn in school). He could not describe any experience that he had after his surgery. Although he could describe facts (semantic memory) that he learned before his operation, he could describe clear memories for only two personal experiences (Corkin, 2013). Another patient, known in the literature as K. C., suffered widespread brain damage after a motorcycle accident, including damage to the hippocampus in both hemispheres, leading to a complete loss of episodic memories (Gao et al., 2020). He could not describe any event in his life, although he remembered factual information. When he looked at old family pictures in a photo album, he identified the people and sometimes the places, but he could not remember anything about the events in the photos (Rosenbaum et al., 2005). These observations tell us that the brain treats episodic memories differently from other memories, and that episodic memories depend on the hippocampus and surrounding areas.

How would memory loss affect someone's ability to imagine the future? If you try to imagine a future event, you build on your memory of similar experiences. Studies using fMRI exhibit that describing past events and imagining future events activate mostly the same areas, including the hippocampus (Addis et al., 2007). Patient K. C. and other people with amnesia have exhibited just as much impairment at imagining the future as at describing the past (Gao et al., 2020; Race et al., 2011). For example, here is part of one patient's attempt to imagine a future visit to a museum (Hassabis et al., 2007, p. 1727):

> Patient: [pause] There's not a lot, as it happens.
> Psychologist: So what does it look like in your imagined scene?
> Patient: Well, there's big doors. The openings would be high, so the doors would be very big with brass handles, the ceiling would be made of glass, so there's plenty of light coming through. Huge room, exit on either side of the room, there's a pathway and map through the center and on either side there'd be the exhibits. [pause] I don't know what they are. There'd be people. [pause] To be honest there's not a lot coming. . . . My imagination isn't. . . well, I'm not imagining it, let's put it that way. . . . I'm not picturing anything at the moment.

When you daydream, what do you think about? Most people think about events in their past, or imaginary events, or possible events in the future. People with hippocampal damage do not. Their mind-wandering is exclusively about the present—another consequence of their lack of episodic memories (McCormick et al., 2018).

The relationship between loss of episodic memory and difficulty imagining the future is theoretically interesting. Have you ever wondered what good is episodic memory? You can remember many events that happened to you years ago, some of them in detail. From an evolutionary standpoint, why did we evolve that ability? What good does it do to be able to remember details of an event that will never happen again? Now we see a possible answer: Remembering those details helps us imagine the future. And if we couldn't imagine the future, we couldn't plan for it.

Better Implicit than Explicit Memory

Nearly all patients with amnesia exhibit better *implicit* than *explicit* memory. **Explicit memory** is deliberate recall of information that one recognizes as a memory, also known as **declarative memory**. If you have an explicit or declarative memory of something, you can state it in words, draw a picture of it, or otherwise demonstrate that you know you remember it. **Implicit memory** is an influence of experience on behavior, even if you do not recognize that influence. For example, H. M. became comfortable and familiar with certain people, such as the psychologists who worked with him over the years, although he did not remember their names or where he had met them. Also, he could not say what topic a recent conversation had discussed, but he might spontaneously start talking about that same topic again (Corkin, 2013).

Another example of implicit memory: As an experiment, three hospital workers agreed to act in special ways toward a patient with amnesia. One worker was as pleasant as possible. The second was neutral. The third was stern, refused all requests, and made the patient perform boring tasks. After 5 days, the patient was asked to look at photos of the three workers and try to identify them or say anything he knew about them. He said he did not recognize any of them. Then he was asked which one he would approach as a possible friend or which one he would ask for help. He was asked this question repeatedly—it was possible to ask repeatedly because he never remembered being asked before—and he usually chose the photo of the "friendly" person and never chose the "unfriendly" person, in spite of the fact that the unfriendly person was a beautiful woman, smiling in the photograph (Tranel and Damasio, 1993). He could not say why he chose to avoid her.

Intact Procedural Memory

Procedural memory, the development of motor skills and habits, is a special kind of implicit memory. You might not be able to describe a motor skill or habit in words, and you might not even think of it as a memory. H. M. learned to read words written backward, as they would be seen in a mirror, although he was surprised at this skill, as he did not remember having tried it before (Corkin, 2002). Patient K. C. had a part-time job at a library where he learned to use the Dewey decimal system in sorting books, but he did not remember when or where he learned that skill (Rosenbaum et al., 2005).

Here is another example of procedural memory: In the video game Tetris, geometrical forms such as □□□ and ┤ fall from the top, and the player must move and rotate them to fill available spaces at the bottom of the screen. People without amnesia improve their skill over a few hours and readily describe the game and its strategy. After playing the same number of hours, patients with amnesia cannot describe the game and say they don't remember playing it. Nevertheless, they slowly improve. Moreover, when they are about to fall asleep, they report seeing images of little piles of blocks falling and rotating (Stickgold et al., 2000). They are puzzled and wonder what these images mean!

People with damage in and around the hippocampus do have one limitation on using their procedural memory: They tend to be less flexible. If they learn one skill and then a second one, they are slower than average on switching back to the first skill (McDougle et al., 2022).

In summary, H. M., K.C., and other patients with similar damage exhibited the following pattern:

- Normal working memory, unless distracted
- Severe anterograde amnesia for declarative memory—that is, difficulty forming new declarative memories
- Severe loss of episodic memories
- Better implicit than explicit memory
- Intact or nearly intact procedural memory

Stop & Check

9. What general point do the studies of H. M. and similar patients tell us about the nature of memory?

See page 405 for the answer.

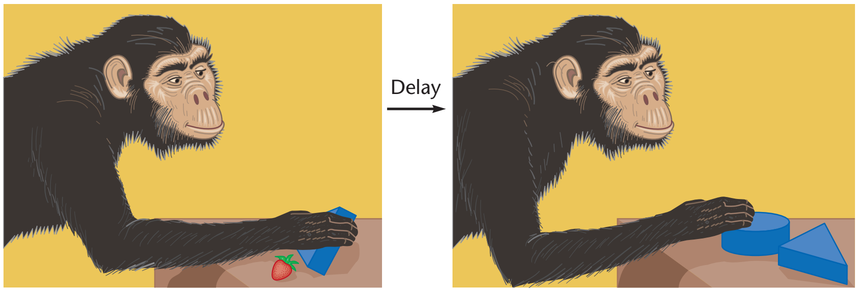
Explaining the Function of the Hippocampus

Exactly how does the hippocampus contribute to memory? Explanations have changed as new evidence has accumulated from research on both humans and laboratory animals.

Part of the answer is that the hippocampus is important for declarative memory (Stein, 1992). In the **delayed matching-to-sample task**, an animal sees an object (the sample) and then, after a delay, gets a choice between two objects, from which it must choose the one that matches the sample. In the **delayed nonmatching-to-sample task**, the procedure is the same except that the animal must choose the object that is different from the sample (Figure 12.9). In both cases, the animal must remember which object was present on this occasion, thereby showing what we might call a declarative memory. Hippocampal damage strongly impairs performance in most cases (Heuer and Bachevalier, 2011; Moore et al., 2012; Zola et al., 2000).

Research of that type fits with human observations that hippocampal damage impairs explicit but not

Figure 12.9 A delayed nonmatching-to-sample task



Monkey lifts sample object to get food.

Food is under the new object.

implicit memory. However, we also know from human observations that the hippocampus relates most strongly to episodic memories. Episodic memories always include context. Think about any of your own episodic memories. They are almost certain to include the location (Robin et al., 2018) and a sequence of events (Buzsaki and Tingley, 2018; Wang et al., 2020). The hippocampus cannot store all that information by itself. Instead, it acts as a coordinator, tying together representations from various cortical areas, in the correct order (Barker et al., 2017; Fortin et al., 2002; Gilmore et al., 2021; Kesner et al., 2002). When people retrieve an episodic memory, activity in and around the hippocampus synchronizes with activity in several cortical areas, consistent with the idea that the hippocampus provides the connections necessary for recall (Watrous et al., 2013).

Your memory of an event changes over time. Think about some experience you had yesterday, perhaps a pizza dinner. Your episodic memory will include much detail—where you were, the time of day, who else was there, who said what, and much more. If you think about a similar event from months ago, you might or might not remember any details. If you do, that memory still depends on your hippocampus. If you have forgotten the details, you still have a generalized memory of the "gist" of what happens at a pizza dinner, and that memory depends largely on the cerebral cortex, although the hippocampus still contributes (Takehara-Nishiuchi and McNaughton, 2008).

At one time, researchers imagined that the hippocampus learned the information first and then transferred the information to the cerebral cortex, losing the contextual details. Later research disconfirmed that idea. The hippocampus does not transfer a memory. Memory representations develop in parallel in the hippocampus and cortex from the start, but the hippocampus stores details whereas the cortex stores semantic information, the gist of the event, and similarities among events (Gilboa and Moscovitch, 2021). As time passes, the hippocampal representation weakens while the representation in the cortex remains. Thus we might form the illusion that the memory transferred from one place to another.

Stop & Check

10. What brain activity occurs when you recall an episodic memory?
11. Why does recent episodic memory include more detail than older memories?

See page 405 for the answer.

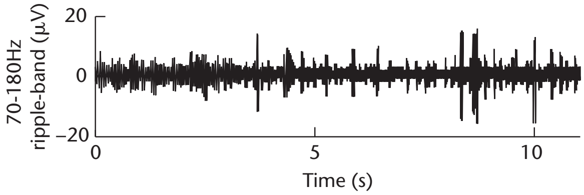
Communication Between Hippocampus and Cortex

Episodic memories depend on an exchange of information between the hippocampus and the cortex (Eichenbaum, 2017). Exchange between hippocampus and cortex also contributes to remembering details of a semantic memory, although semantic memory can continue after hippocampal damage. To reactivate a memory, the hippocampus and cerebral cortex bounce messages back and forth with **sharp-wave ripples**, illustrated in Figure 12.10 (Norman et al., 2021). Much slower oscillations also occur (Kota et al., 2020).

Researchers recorded from the hippocampus and cortex of 20 patients while they were undergoing brain surgery for control of epilepsy. (Brain surgery can be done under local anesthesia.) The patients answered true/false questions about experiences they might have had at various times from today to last month, as well as semantic questions. Hippocampal ripples increased most strongly when patients answered autobiographical questions, especially when the answer was "yes." That result implies that the ripples help to reexperience an event. The ripples lasted longer when people took longer to reply and when they were recalling older events, suggesting that the ripples represent efforts to recall something. The

Figure 12.10 An example of sharp-wave ripples from the hippocampus

The ripples, high-frequency oscillations, communicate between hippocampus and cortex to access a memory.



pattern of ripples when recalling older events resembled in some ways the pattern when people were answering semantic questions. That observation fits with the fact that older memories resemble something that you "know" instead of something you are actively reexperiencing (Norman et al., 2021). Other studies found that the ripple patterns during memory recall often resemble those that occurred during original learning, again confirming that the ripples help to reexperience an event (Vaz et al., 2020).

Stop & Check

12. What evidence indicates that hippocampal ripples represent efforts to remember something?

See page 405 for the answer.

Navigation

Another line of research explores the role of the hippocampus in perceiving location in time and space. First consider studies using a **radial maze** with several arms—typically eight—some or all of which have a bit of food at the end (Figure 12.11). A rat's best strategy is to explore each arm once and only once, remembering where it has already gone. In a variation of the task, a rat might learn that the arms with a rough floor never have food or that the arms pointing toward the window never have food. Thus, a rat can make a mistake either by entering a never-correct arm or by entering any arm more than once.

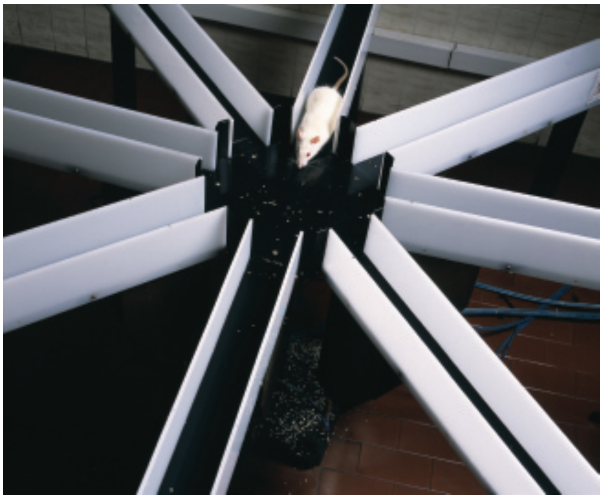
Rats with damage to the hippocampus can learn to avoid the never-correct arms, but even after much training they often enter a correct arm twice. They forget which arms they have already tried (Jarrard et al., 1984; Olton and Papas, 1979; Olton et al., 1978).

In the **Morris water maze**, a rat swims through murky water to find a rest platform that is just under the surface (Figure 12.12). (Rats swim only when necessary. Humans are among the few land mammals that swim voluntarily.) A rat with hippocampal damage slowly learns to find the platform if it always starts from the same place and can always turn the same direction to find the rest platform. However, if it starts from different locations or if the rest platform occasionally moves from one location to another, the rat is disoriented (Eichenbaum, 2000; Liu and Bilkey, 2001). Evidently the hippocampus is essential for remembering locations.

The hippocampus is important for spatial orientation in humans as well. Researchers conducted PET scans on the brains of London taxi drivers as they answered navigation questions such as, "What's the shortest legal route

Figure 12.11 A radial maze

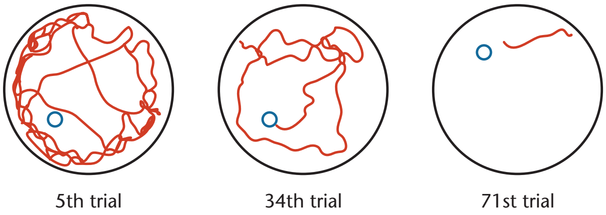
A rat that reenters one arm before trying other arms has made an error of spatial working memory.



Mauro Fermariello/Science Source

Figure 12.12 The Morris water maze

An intact rat learns by trial and error. In each case the line traces the path a rat took to the platform, marked by a circle. On the fifth trial, the rat stayed mainly near the edge and never found the platform. On the 34th trial, it found the platform in 35 seconds. On the 71st trial, it went directly to the platform in 6 seconds.



(**Source:** From "Response learning of rats in a Morris water maze: Involvement of the medial prefrontal cortex," by J. P. C. de Bruin, W. A. M. Swinkels, and J. M. de Brabander, 1997, *Behavioral Brain Research, 85,* 47–55.)

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from the Carlton Tower Hotel to the Sherlock Holmes Museum?" London taxi drivers are well trained and answer with impressive accuracy. Answering these questions activated their hippocampus, and MRI scans revealed that they have a larger than average posterior hippocampus. The longer they had been taxi drivers, the larger their posterior hippocampus (Maguire et al., 2000). This result suggests growth of the adult human hippocampus in response to spatial learning experiences.

A major advance in our understanding came from single-cell recordings. May-Britt Moser, Edvard Moser, and John O'Keefe shared the 2014 Nobel Prize in Physiology or Medicine for their discovery of the cells responsible for spatial memory.

The research began with the discovery of **place cells**, hippocampal neurons that respond when an animal is in a particular location and looking in a particular direction (O'Keefe and Burgess, 1996; O'Keefe and Dostrovsky, 1971). These cells modify their responses depending on the environment. For a laboratory rat in a small enclosure, each place cell responds to a small area, but for a bat in flight, place cells respond to much larger areas (Eliav et al., 2021). When an animal moves to a different environment, the cells reorder themselves to map out the new locations. If a rat explores a three-dimensional lattice, the grid cells become variable in size and shape (Grieves et al., 2021). If an animal has received a reward in a particular place, it reorients its place cells to provide more detail near the reward (Boccara et al., 2019). If an animal has run through a maze for reward so many times in one session that it is losing interest, the place cells become less responsive (Pettit et al., 2022).

When an animal is moving, place cells anticipate the next places it will go (Dotson and Yartsev, 2021; Payne et al., 2021). That fact enables researchers to "read a rat's mind" to a limited degree. Suppose a rat is at a choice point in a difficult maze. It stops and looks one way and then the other a few times before proceeding. Recordings from its hippocampus show that cells become active in the proper order as if the rat were walking down one path or the other. We can watch the brain activity as the rat imagines trying each route (Redish, 2016). A rat that received a shock at one point along a track activates a sequence of place cells from its current location to the dangerous area, apparently imagining the route, and then avoids it (Wu et al., 2017). People sometimes assert that humans are the only species that can imagine the future. Wrong. Even rats can, at least for the very near future. We get similar results from human brains while people imagine moving from one place to another (T. I. Brown et al., 2016; Jacobs et al., 2013; J. F. Miller et al., 2013).

Many place cells also function as **time cells** that respond at a particular point in a sequence of time. Consider a rat that has to run on a treadmill for 20 seconds to receive reward. Many hippocampal cells become active at a particular time during the 20 seconds (Salz et al., 2016). In another study, rats had to run to a certain point and then pause for at least six seconds, with no external signal, and then run the rest of the route. Cells feeding into the hippocampus were active at specific times during the delay (Heys and Dombeck, 2018). A general way to describe hippocampal function is that it encodes sequences—ordered sequences of places, times, or actions.

Hippocampal place cells receive much of their input from the nearby entorhinal cortex (Figure 12.8). When researchers recorded from cells in the entorhinal cortex, they found results like the ones in Figure 12.13. Each cell became active at locations separated from one another in a hexagonal grid. The cells are therefore called **grid cells**. At a given level within the entorhinal cortex, different cells respond to different sets of locations, but always in a hexagon, at least when an animal is exploring a two-dimensional space. Cells at more dorsal levels (shown left to right in Figure 12.13) respond to larger areas (Stensola et al., 2012). Many of the cells respond to a combination of the animal's location and the direction it is heading (Sargolini et al., 2006). Some cells respond to the animal's speed of locomotion instead of its location or direction (Kropff et al., 2015; Munn et al., 2020). The animal determines its location and direction from a combination of inputs from several populations of cells.

The place cells and time cells of the hippocampus relate to the previous discussion of episodic memory. Any episodic memory refers to events that occurred in a particular place, with a particular sequence of events over time. Memories include spatial information even when it seems irrelevant (Foster et al., 2017). If you are trying to remember a graph in your math book, you might remember that it was in the upper left-hand corner of the page. If you are trying to remember something from a lecture, you might remember where you were sitting when you heard it.

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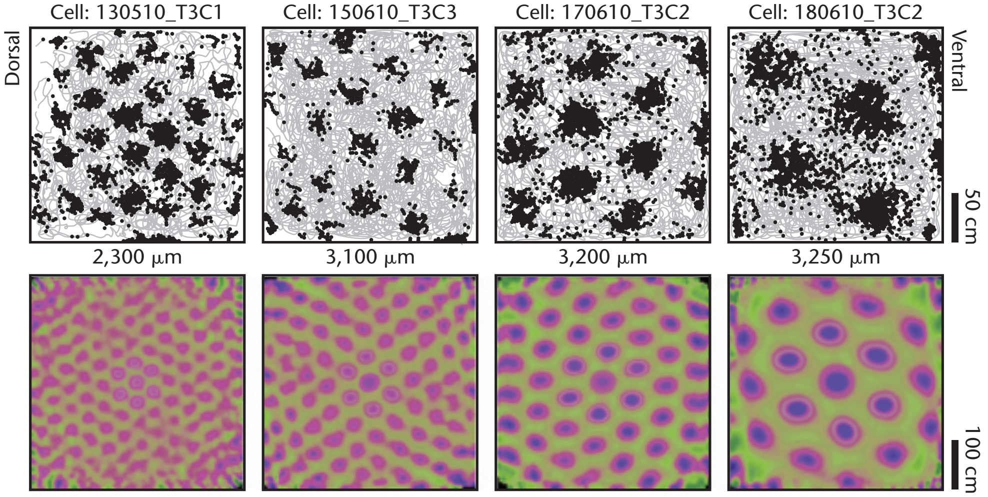
European Pressphoto Agency/
LUND/Sweden/Newscom

May-Britt Moser and Edvard Moser

> Like the GPS in our phones and cars, our brain's system assesses where we are and where we are heading by integrating multiple signals relating to our position and the passage of time.... The ability to figure out where we are and where we need to go is key to survival. Without it, we, like all animals, would be unable to find food or reproduce. Individuals—and, in fact, the entire species—would perish. (Moser and Moser, 2016, p. 26)

Figure 12.13 Recordings from four cells in a rat's entorhinal cortex

Each box represents one cell, and each dot within a box represents a location where that cell responded. Each cell responded to locations arranged in a hexagon. Cells at a more dorsal level in the entorhinal cortex (toward the right) had wider spacing of grids.



(**Source:** From "The entorhinal grid map is discretized," by H. Stensola, T. Stensola, T. Solstad, K. Frøland, M.-B. Moser, and E. I. Moser, 2012, *Nature, 492,* 72–78.)

Stop & Check

13. In addition to an animal's location, what else do many place cells monitor?
14. What is the evidence that rats can imagine the future?
15. How do place cells and time cells relate to episodic memory?

See page 405 for the answer.

The Striatum

Part of the basal ganglia known as the **striatum** (or dorsal striatum), consisting of the caudate nucleus and the putamen (Figure 7.16), controls aspects of memory different from those of the hippocampus. One way to state the distinction is that the hippocampus learns declarative memories and the striatum learns habits. When you learned to button your shirt or blouse as a child, at first you had to think about it step by step, but by now you do it without much thought, and you might find it difficult to describe the process in words. The same is true for tying your shoestrings, signing your name, playing your favorite video game, and much more. Habits develop slowly and depend on the striatum. Recall the discussion of infant amnesia in the first module. We forget the episodic memories of infancy, but not the habits and skills we learned then. There are two reasons: One, we continue practicing those skills and habits. Two, the habits and skills depend on the striatum, not the hippocampus where so many new neurons are forming.

Once a habit is established, it does not require consistent reinforcement, and it can be hard to inhibit. You are riding an elevator, the door opens, and you automatically step out. Oops, wrong floor. You are in your car waiting for the light to change when the left-turn light turns green. You start going forward. Oops, that light isn't for my lane. Habits become almost automatic (Tricomi et al., 2009).

Another way to state the distinction is that the hippocampus orients behaviors toward external landmarks and the striatum orients behaviors relative to your body. If you learn "when you hear a chime, turn toward the clock," that behavior depends mostly on the hippocampus and related structures. If you learn "when you hear a chime in this location, turn to the right," that depends more on the striatum (Geerts et al., 2020). Learning to turn a particular direction develops slowly, like other habits.

The striatum is also specialized for **probabilistic learning**, or statistical learning—learning what will probably happen under certain circumstances, or what to expect when the outcome is not entirely predictable. You consider many types of information when you conclude that it will probably rain, or that your mother probably wouldn't enjoy the movie you just saw, or that someone you just met might go out on a date with you. You might not be able to explain how you decided.

To illustrate, consider the following example. In each of 38 cases you have three pieces of information, here illustrated as gray or purple rectangles. Based on that information, guess whether it will rain tomorrow ("yes") or not ("no"). You are provided with the correct answer for the first 36. You will get the idea of the task best if you try the items one at a time. What do you guess for the final two items, and on what basis did you make that decision?

Try It Yourself

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□	□	□	YES	□	■	□	YES
■	■	■	NO	■	□	□	YES
□	■	□	YES	□	□	■	NO
□	■	■	YES	□	■	□	YES
■	□	■	NO	■	■	□	YES
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■	□	□	YES	□	■	□	YES
□	□	■	NO	□	■	■	YES
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□	□	□	YES	□	□	□	YES
□	■	■	YES	■	■	□	NO
■	■	■	NO	□	■	□	?
■	□	■	NO	□	■	■	?

In this task, you could develop any of several strategies. If you simply noticed that the answer is yes more often than no, you could always answer yes, being correct 64 percent of the time. A better strategy is, when you see more gray than purple rectangles, guess yes, and if you see more purple than gray rectangles, guess no. That strategy is correct 83 percent of the time. If you pay attention to just one column, your accuracy could vary from 53 to 86 percent correct, depending on which column you choose. The best strategy is complicated: If you see more gray than purple rectangles, guess yes; if you see more purple than gray rectangles, guess no, except that if it goes "gray-purple-purple," guess yes, and if it goes "gray-gray-purple," guess no. That strategy gives a correct answer 94 percent of the time with the material exhibited here. (The answers for the final two items are YES, YES.)

You are beyond amazing if you figured out that last strategy from the trials given here. But if you had the patience to continue for hundreds of trials, your accuracy would eventually, gradually climb up toward 94 percent correct. You might not be able to describe your strategy. You would just "know" the right answer to guess each time. Gradual learning of probabilistic information depends on the striatum.

Suppose we run a test like this on people with Parkinson's disease, who have damage in the striatum. They perform about the same as people without Parkinson's disease at first, because their intact hippocampus enables them to learn declarative facts such as "gray means yes and purple means no." However, they do not show gradual improvement over later trials, because that depends on the striatum. If they can't form an explicit, declarative memory, they don't improve at all (Moody et al., 2010).

People with amnesia after hippocampal damage are the opposite. They perform randomly on a task like this at first, because they cannot form declarative memories that mostly gray or mostly purple symbols mean anything. However, if they continue for a long time, they do improve, based on habits supported by the striatum (Bayley et al., 2005; Palombo et al., 2021; Shohamy et al., 2008). Healthy people under great stress or distraction also learn slowly or rely on old habits, like people with a damaged hippocampus (Brown et al., 2020; Foerde et al., 2006).

Table 12.1 summarizes the distinction between the hippocampus and the striatum (Balleine et al., 2007; Foerde et al., 2013; Foerde and Shohamy, 2011; Koralek et al., 2012; Shohamy, 2011; Wan et al., 2012). However, the separation between the two systems is not complete. Nearly all learned tasks activate both systems somewhat (Albouy et al., 2008; Ferbinteanu, 2020).

Stop & Check

16. Would Parkinson's disease patients be more impaired at learning new facts or at acquiring new habits?
17. In probabilistic learning situations, how does initial learning differ from later learning?

See page 405 for the answer.

Table 12.1 | Brain Areas for Two Types of Learning

	Hippocampus	Striatum
Type of learning	Declarative, explicit	Habits, implicit, often hard to express in words
Speed of learning	Can be single-trial	Slow, gradual
Way of orienting behaviors	Relative to external landmarks	Relative to the body
Reaction to probabilistic information	Quickly notices the main pattern	Gradually learns to weigh many types of information
How easily changed?	Can update based on new information	Slow to change and difficult to inhibit
Result of damage	Impaired declarative memory, especially episodic memory	Impaired learning of skills and habits

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Cortical Areas

Other brain areas contribute to learning and memory in various ways. When investigators asked two patients with parietal lobe damage to describe certain events, their episodic memory appeared sparse, with almost no details. Then the investigators asked follow-up questions, such as, "Where were you?" and "Who else was there at the time?" To these questions the patients answered correctly and in reasonable detail, indicating that their episodic memories were intact, as well as their speech and their willingness to cooperate. What was lacking was their ability to elaborate on a memory spontaneously (Berryhill et al., 2007). Later research applied a magnet to the scalp of people in a way that temporarily inactivated part of the parietal cortex called the angular gyrus. The procedure affected only episodic memories. People volunteered few details when describing their experiences, although they could answer questions normally. Furthermore, they tended to describe the experiences from a third-person perspective, as if they had happened to someone else. Apparently the angular gyrus is important for the subjective experience of remembering something, the experience of "re-living" it (Bonnici et al., 2018).

People with atrophy in the temporal cortex suffer **semantic dementia**, a loss of semantic memory. One patient while riding down a road saw some sheep and asked what they were. The problem wasn't with the word *sheep.* It was as if he had never seen a sheep before. When another person saw a picture of a zebra, she called it a horse but then pointed at the stripes and asked what "those funny things" were. She had lost the concept of zebra. Such patients often forget the typical color of common fruits and vegetables (Patterson et al., 2007). Their vision is intact, as they can copy a drawing accurately. They just don't know what the drawing means. In many cases they also lose the ability to recognize the meaning of sounds, smells, and tastes. Semantic dementia varies depending on the location and amount of atrophy, and it differs depending on whether the damage is mostly in the left or right hemisphere, and mostly anterior or posterior temporal cortex (Snowden et al., 2018).

Module 12.2 | In Closing

Brain Damage and Memory

The most obvious thing that brain damage tells us about memory is that we have several types of memory. It is possible to impair just episodic memory or just habit formation. It is possible to remember old semantic memories without being able to store new ones. It is possible to impair the ability for gradual learning of probabilistic information, without impairing the ability to learn something quickly. It is possible to see objects without remembering what they are or what they mean. Memory is a family of related functions, not a single entity.

Summary

1. People with damage to the hippocampus have great trouble forming new long-term declarative memories, especially episodic memories. They also have trouble imagining the future. **395**
2. People with damage to the hippocampus nevertheless show implicit memory, short-term memories, and procedural memories. **395, 398**
3. Memories form simultaneously in the hippocampus and the cerebral cortex. The hippocampus stores episodic details. The cerebral cortex stores more general information. As the store in the hippocampus tends to fade over time, memory of an event becomes more gist-like. **399**
4. High-frequency sharp-wave ripples communicate between hippocampus and cortex to recall a memory. The ripples last longer when a memory is more difficult to recall. **399**
5. The hippocampus is also important for spatial orientation and for monitoring memories of sequences of places, times, or actions. **400**
6. The hippocampus contains place cells. Monitoring those cells shows that animals can imagine traveling in one path or another. **401**
7. Place cells receive input from grid cells in the entorhinal cortex. Grid cells respond to a series of locations arranged in a hexagonal grid. **401**
8. Whereas the hippocampus is important for rapid storage of an event, the striatum (part of the basal ganglia) is important for gradually developing habits, for orienting behaviors relative to your body, and for probabilistic learning. **402**
9. As a habit forms, it depends at first on the hippocampus but after much practice it becomes more dependent on the striatum. **403**

10. Part of the parietal cortex is important for the subjective experience of reliving a memory. **404**
11. Damage in the temporal lobe can led to semantic dementia, characterized by loss of understanding of what things are or what they mean. **404**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

anterograde amnesia	**395**
declarative memory	**398**
delayed matching-to-sample task	**398**
delayed nonmatching-to-sample task	**398**
episodic memory	**397**
explicit memory	**398**
grid cells	**401**
implicit memory	**398**
Morris water maze	**400**
place cells	**401**
probabilistic learning	**402**
procedural memory	**398**
radial maze	**400**
retrograde amnesia	**395**
semantic dementia	**404**
semantic memories	**397**
sharp-wave ripples	**399**
striatum	**402**
time cells	**401**

Thought Questions

1. From what you know about human infants, which type of memory would you guess develops first, the hippocampal-dependent system or the striatum-dependent system?
2. Is there an adaptive reason for having a more detailed episodic memory for recent events than for older ones? Why did our evolution develop this way?

Stop & Check Answers

9. Episodic memory differs from semantic memory, explicit memory differs from implicit memory, and declarative memory differs from procedural memory. In each case, brain damage can impair one without the other.
10. The hippocampus retrieves information from cortical areas in the proper sequence.
11. The hippocampus stores detailed episodic memories, and the cortex stores semantic memories and general relationships. As time passes, the hippocampal representation fades.
12. The ripples last longer when people recall an autobiographical event, and especially when they have to struggle to recall it.
13. Some also respond to time or the direction the animal is heading.
14. When a rat pauses at a choice point in a maze, place cells respond in sequence as if the animal were traveling down one arm or another of the maze.
15. Episodic memories almost always include the location of the remembered event, and often the approximate time as well.
16. Parkinson's disease patients are more impaired at acquiring new habits. Habit learning depends on the striatum more than the hippocampus, and the striatum is damaged in Parkinson's disease.
17. At first, responding depends on declarative memory controlled by the hippocampus. After extensive practice, the striatum develops habits of responding that weigh many types of information to produce the most accurate responding.

Module 12.2 | End-of-Module Quiz

1. What is anterograde amnesia?
   - **a.** Loss of factual memory
   - **b.** Loss of memory for personal experiences
   - **c.** Loss of memory for space and time
   - **d.** Inability to form new memories

2. Which of these is most impaired in patients with hippocampal damage?
   - **a.** Ability to imagine the future
   - **b.** Ability to learn motor habits
   - **c.** Implicit memory
   - **d.** Working memory

3. Which of the following was most severely impaired in patient H. M.?
   - **a.** Episodic memory
   - **b.** Procedural memory
   - **c.** Implicit memory
   - **d.** Short-term memory

4. What type of memory does the delayed match to sample task measure?
   - **a.** Probabilistic memory
   - **b.** Procedural memory
   - **c.** Implicit memory
   - **d.** Declarative memory

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5. How does memory storage in the hippocampus relate to memory storage in the cortex?

- **a.** They develop in parallel from the start.
- **b.** The hippocampus slowly transfers memories to the cortex.
- **c.** The cortex slowly transfers memories to the hippocampus.
- **d.** Every memory depends on one or the other, not both.

6. What do the sharp-wave ripples in the hippocampus apparently indicate?

- **a.** Responses to a magnetic field
- **b.** A combination of visual and auditory information
- **c.** Effort to recall a memory
- **d.** Feedback on whether an answer is correct

7. What type of memory do the radial maze and Morris water maze test?

- **a.** Episodic memory
- **b.** Verbal memory
- **c.** Social memory
- **d.** Spatial memory

8. Evidence that rats can imagine the future came from recordings from what type of cell?

- **a.** Glia cells
- **b.** Place cells
- **c.** Dorsal striatum cells
- **d.** Visual cortex cells

9. Why are certain cells in the entorhinal cortex called grid cells?

- **a.** They respond to locations distributed in a hexagonal grid.
- **b.** They have axons that spread out in the shape of a grid.
- **c.** They have dendrites that spread out in the shape of a grid.
- **d.** They respond when an animal sees something shaped like a grid.

10. The striatum is primarily responsible for which type of learning?

- **a.** Gradually learning habits
- **b.** Acquiring and storing episodic memories
- **c.** Memories that people can easily describe in words
- **d.** Quickly adapting learned behaviors to new circumstances

11. Which brain area is most important for gradual probabilistic learning?

- **a.** Hippocampus
- **b.** Striatum
- **c.** Parietal cortex
- **d.** Locus coeruleus

12. If someone can answer questions about personal experiences, but never volunteers much about them, and describes them as if they happened to someone else, where is the probable damage?

- **a.** Hippocampus
- **b.** Striatum
- **c.** Parietal cortex
- **d.** Locus coeruleus

Answers: 1d, 2a, 3a, 4d, 5a, 6c, 7d, 8b, 9a, 10a, 11b, 12c.

Module 12.3

Cellular Mechanisms of Memory

Learning Objectives

After studying this module, you should be able to:

10. Define Hebbian synapses.
11. Explain what we learned about memory from studies of *Aplysia*.
12. Explain the mechanism of long-term potentiation.
13. Evaluate attempted methods of improving memory.

Neurons communicate with one another, and learning necessarily means a change in that communication. Much depends on synapses, although changes in cell bodies and axons contribute also (Lisman et al., 2018; Pan et al., 2020). The task of discovering and understanding these microscopic events is a challenging one, and researchers have explored many avenues that seemed promising for a while but now seem fruitless.

Blind Alleys and Abandoned Mines

Textbooks, including this one, concentrate mostly on successful research that led to our current understanding of a field. You may get the impression that science progresses smoothly, with each experiment contributing to the body of knowledge. However, if you look at old journals or textbooks, you will find discussions of many "promising" or "exciting" findings that we disregard today. Scientific research does not progress straight from ignorance to enlightenment. It explores one direction after another, a little like a rat in a complex maze, abandoning the dead ends and pursuing arms that lead further. The problem with the maze analogy is that an investigator seldom runs into a wall that clearly identifies the end of a route. A better analogy is a prospector digging for gold, never certain whether to abandon an unprofitable spot or to keep digging just a little longer.

Many previously exciting lines of research in the study of learning are now of little more than historical interest. Here are three examples:

1. Wilder Penfield sometimes performed brain surgery for severe epilepsy on conscious patients, using only scalp anesthesia. When he applied a brief, weak electrical stimulus to part of the brain, the patient could describe the experience that the stimulation evoked. Stimulation of the temporal cortex sometimes evoked vivid descriptions such as:

   I feel as though I were in the bathroom at school.
   I see myself at the corner of Jacob and Washington in South Bend, Indiana.
   I remember myself at the railroad station in Vanceburg, Kentucky; it is winter and the wind is blowing outside, and I am waiting for a train.

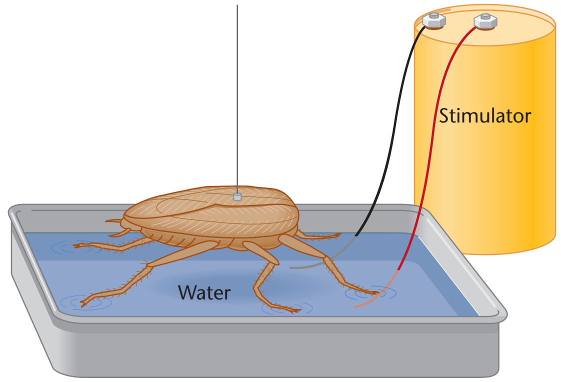
   Penfield (1955; Penfield and Perot, 1963) suggested that each neuron stores a particular memory, like a videotape of one's life. However, brain stimulation rarely elicited a memory of a specific event. Usually, it evoked vague sights and sounds, or recollections of common experiences such as "seeing a bed" or "hearing a choir sing 'White Christmas.'" Stimulation almost never elicited memories of doing anything—just of seeing and hearing. Also, some patients reported events that they had never actually experienced, such as being chased by a robber or seeing Christ descend from the sky. In short, the stimulation produced something more like a dream than a memory.
2. G. A. Horridge (1962) apparently demonstrated that decapitated cockroaches can learn. First he cut the connections between a cockroach's head and the rest of its body. Then he suspended the cockroach so that its legs dangled just above a surface of water. An electrical circuit was arranged as in Figure 12.14 so that the roach's leg received a shock whenever it touched the water. Each experimental roach was paired with a control roach that got a leg shock whenever the first roach did. Only the experimental roach had any control over the shock, however. This kind of experiment is known as a "yoked-control" design.

   Over 5 to 10 minutes, headless roaches in the experimental group increased a response of tucking the leg under the body to avoid shocks. Those in the control group did not, on average, change their leg position. Thus, the changed response apparently qualifies as learning and not as an accidental by-product of the shocks.

   These experiments initially seemed a promising way to study learning in a simple nervous system

Figure 12.14 Learning in a headless cockroach?

The decapitated cockroach, suspended just above the water, receives a shock whenever its hind leg touches the water. A cockroach in the control group gets a shock whenever the first roach does regardless of its own behavior. According to some reports, the experimental roach learned to keep its leg out of the water.



(**Source:** From "Learning of leg position by the ventral nerve cord in headless insects," by G. A. Horridge, *Proceedings of the Royal Society of London, B, 157,* 1962, 33–52. Copyright © 1962 The Royal Society of London. Reprinted by permission of the Royal Society of London and G. A. Horridge.)

(Eisenstein and Cohen, 1965). Unfortunately, decapitated cockroaches learn slowly—yeah, I think you could have guessed that—and the results vary sharply from one individual to another, limiting the usefulness of the results. After a handful of studies, interest in this line of research faded.

3. In the 1960s and early 1970s, several investigators proposed that each memory is coded as a specific molecule, probably RNA or protein. The boldest test of that hypothesis was an attempt to transfer memories chemically from one individual to another. James McConnell (1962) reported that, when planaria (flatworms) cannibalized other planaria that had been classically conditioned to respond to a light, they apparently remembered what the cannibalized planaria had learned. At least they learned the response faster than average.

Inspired by that report, other investigators trained rats to approach a clicking sound for food (Babich et al., 1965). After the rats were well trained, the experimenters ground up their brains, extracted RNA, and injected it into untrained rats. The recipient rats reportedly learned to approach the clicking sound faster than rats in the control group did.

That report led to a wealth of studies on the transfer of training by brain extracts. In *some* of these experiments, rats that received brain extracts from a trained group showed apparent memory of the task, whereas those that received extracts from an untrained group did not (Dyal, 1971; Fjerdingstad, 1973). The results were inconsistent and unreplicable, however, even within a single laboratory (Smith, 1975). Many laboratories failed to find any hint of a transfer effect. Furthermore, theoretically there was no good reason to expect this procedure to work. By the mid-1970s, most researchers saw no point in continuing this research, and funding agencies refused to consider further grants for it.

Learning and the Hebbian Synapse

Research on the physiology of learning began with Ivan Pavlov's concept of classical conditioning. Although that theory led Karl Lashley to an unsuccessful search for connections in the cerebral cortex, it also stimulated Donald Hebb to propose a mechanism for change at a synapse.

Hebb suggested that when the axon of neuron A "repeatedly or persistently takes part in firing [neuron B], some growth process or metabolic change takes place in one or both cells" that increases the subsequent ability of axon A to excite cell B (Hebb, 1949, p. 62). In other words, an axon that has been paired with strong depolarization of the postsynaptic neuron becomes more successful in the future. In still simpler words, "cells that fire together wire together." Later researchers slightly modified this idea: Neurons that are near each other and fire together wire together (Ascoli, 2015). That saying is less catchy, but it acknowledges that the structure of the nervous system determines which connections are possible.

© Mary Ellen Hebb

Donald O. Hebb (1904–1985)

Modern psychology takes completely for granted that behavior and neural function are perfectly correlated. . . . There is no separate soul or life force to stick a finger into the brain now and then and make neural cells do what they would not otherwise. . . . It is quite conceivable that some day the assumption will have to be rejected. But it is important also to see that we have not reached that day yet. . . . One cannot logically be a determinist in physics and chemistry and biology, and a mystic in psychology. (Hebb, 1949, p. xiii)

Consider how this process relates to classical conditioning. Suppose axon A initially excites cell B slightly, and axon C excites B more strongly. If A and C fire together, their combined effect on B may produce an action potential. You might think of axon A as the conditioned stimulus and axon C as the unconditioned stimulus. Pairing activity in axons A and C increases the future effect of A on B. A **Hebbian synapse** is one that increases its effectiveness because of simultaneous activity in the presynaptic and postsynaptic neurons. Such synapses are essential for many kinds of associative learning.

Stop & Check

18. How can a Hebbian synapse account for the basic phenomena of classical conditioning?

See page 415 for the answer.

Single-Cell Mechanisms of Invertebrate Behavior Change

If you want to look for a needle in a haystack, a good strategy is to look in a small haystack. Many researchers have turned to studies of invertebrates. Vertebrate and invertebrate nervous systems are organized differently, but the chemistry of the neuron, the principles of the action potential, the neurotransmitters, and their receptors are the same. If we identify the physical basis of learning and memory in an invertebrate, we have at least a hypothesis of what might work in vertebrates. Biologists have long used this strategy for studying genetics, embryology, and other biological processes.

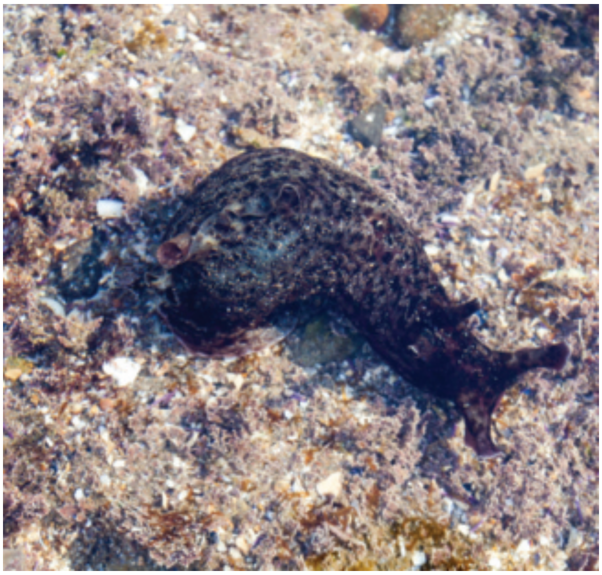
Aplysia as an Experimental Animal

Aplysia, a marine invertebrate related to slugs, has been a popular animal for studies of the physiology of learning (Figure 12.15). Compared to vertebrates, it has fewer neurons, many of which are large and easy to study. Unlike vertebrates, *Aplysia* neurons are virtually identical from one individual to another so that investigators can replicate one another's work in detail.

Much research deals with the withdrawal response: Any touch to the siphon, mantle, or gill of an *Aplysia* (Figure 12.16) evokes a withdrawal response of the irritated

Figure 12.15 *Aplysia*, a marine mollusk

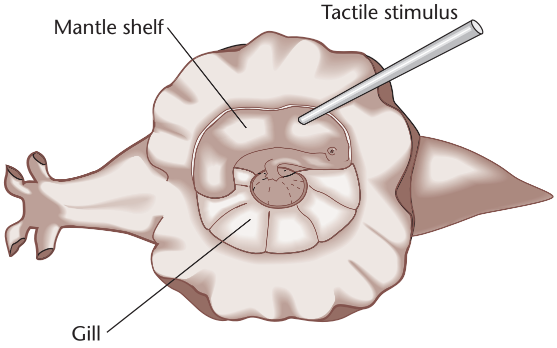
The aplysia, which is slightly larger than a human hand, is a popular animal for studies of the physiology of learning.



Heather Lucia Snow/Shutterstock.com

Figure 12.16 Touching an *Aplysia* causes a withdrawal response

The sensory and motor neurons controlling this reaction have been identified and studied.



John Lamparski/Getty Images Entertainment/Getty Images

Eric R. Kandel

> The questions posed by higher cognitive processes such as learning and memory are formidable, and we have only begun to explore them. Although elementary aspects of simple forms of learning have been accessible to molecular analysis in invertebrates, we are only now beginning to know a bit about the genes and proteins involved in more complex, hippocampus-based learning processes of mammals. (Kandel, personal communication)

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structure. Investigators have traced the neural path from the touch receptors through other neurons to the motor neurons. Using this neural pathway, investigators have studied learned changes in behavior. In 2000, Eric Kandel won a Nobel Prize for this work.

Habituation in *Aplysia*

Habituation is a decrease in response to a repeated stimulus that is accompanied by no change in other stimuli. For example, a sudden noise may startle you, but you respond less after repeated presentations. If we repeatedly stimulate an *Aplysia*'s gills with a brief jet of seawater, it withdraws at first, but after many repetitions, it stops responding. The decline in response is not due to muscle fatigue; even after habituation has occurred, direct stimulation of the motor neuron produces a full-size muscle contraction (Kupfermann et al., 1970). We can also rule out changes in the sensory neuron. The response in the sensory neuron is the same as before, but it produces less excitation in the motor neuron (Kupfermann et al., 1970). We are therefore left with the conclusion that habituation in *Aplysia* depends on a change in a synapse between the sensory neuron and the motor neuron (Figure 12.17).

Sensitization in *Aplysia*

If you experience an unexpected sharp pain, you temporarily react more strongly than usual to other sudden stimuli. This phenomenon is **sensitization**, an increase in response to mild stimuli, caused by exposure to more intense stimuli. Similarly, a strong stimulus almost anywhere on *Aplysia*'s skin intensifies a later withdrawal response to a touch.

Researchers traced sensitization to changes at identified synapses (Cleary et al., 1989; Dale et al., 1988; Kandel and Schwartz, 1982). Strong stimulation on the skin excites a *facilitating interneuron* that releases serotonin onto the presynaptic terminals of many sensory neurons. Serotonin blocks potassium channels in these membranes. Because potassium now flows more slowly out of the cell, the membrane repolarizes more slowly after an action potential. Therefore, the presynaptic neuron continues releasing its neurotransmitter for longer than usual. Repeating this process causes the sensory neuron to synthesize new proteins that produce long-term sensitization (Bailey et al., 2000). This research shows how it is possible to explain one example of behavioral plasticity in terms of molecular events. Other studies explored mechanisms of classical and instrumental conditioning in *Aplysia*.

Stop & Check

19. When serotonin blocks potassium channels on the presynaptic terminal, what is the effect on transmission?

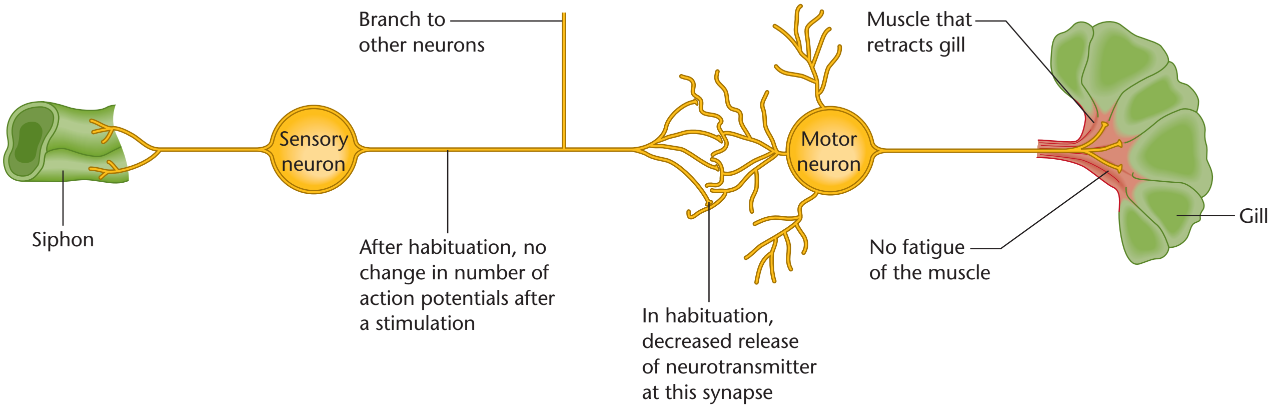
See page 415 for the answer.

Long-Term Potentiation in Vertebrates

Neuroscientists have long assumed that learning depends on changes at synapses, and the work on *Aplysia* supports that idea. The first evidence for a similar process among vertebrates came from studies of neurons in the rat hippocampus (Bliss and Lømo, 1973). The phenomenon, known as **long-term potentiation (LTP)**, is this: One or more axons connected to a dendrite bombard it with a rapid series of stimuli. The burst of intense stimulation leaves some of the synapses potentiated (more responsive to new input) for minutes, days, or weeks.

Figure 12.17 Habituation of the gill-withdrawal reflex in *Aplysia*

Touching the siphon causes gill withdrawal. After many repetitions, the response habituates because of decreased transmission at the synapse between the sensory neuron and the motor neuron.


Branch to other neurons
Muscle that retracts gill
Sensory neuron
Motor neuron
Siphon
Gill
After habituation, no change in number of action potentials after a stimulation
No fatigue of the muscle
In habituation, decreased release of neurotransmitter at this synapse

(**Source:** Redrawn from "Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in aplysia," by V. Castellucci, H. Pinsker, I. Kupfermann, and E. Kandel, *Science, 1970,* 167, 1745–1748. Copyright © 1970 by AAAS. Used by permission of AAAS and V. Castellucci.)

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LTP shows three properties that make it an attractive candidate for a cellular basis of learning and memory:

- **specificity**—If some of the synapses onto a cell have been highly active and others have not, only the active ones become strengthened.
- **cooperativity**—Nearly simultaneous stimulation by two or more axons produces LTP more strongly than does repeated stimulation by just one axon.
- **associativity**—Pairing a weak input with a strong input enhances later response to the weak input, as illustrated in Figure 12.18. In this regard, LTP matches what we would expect of Hebbian synapses.

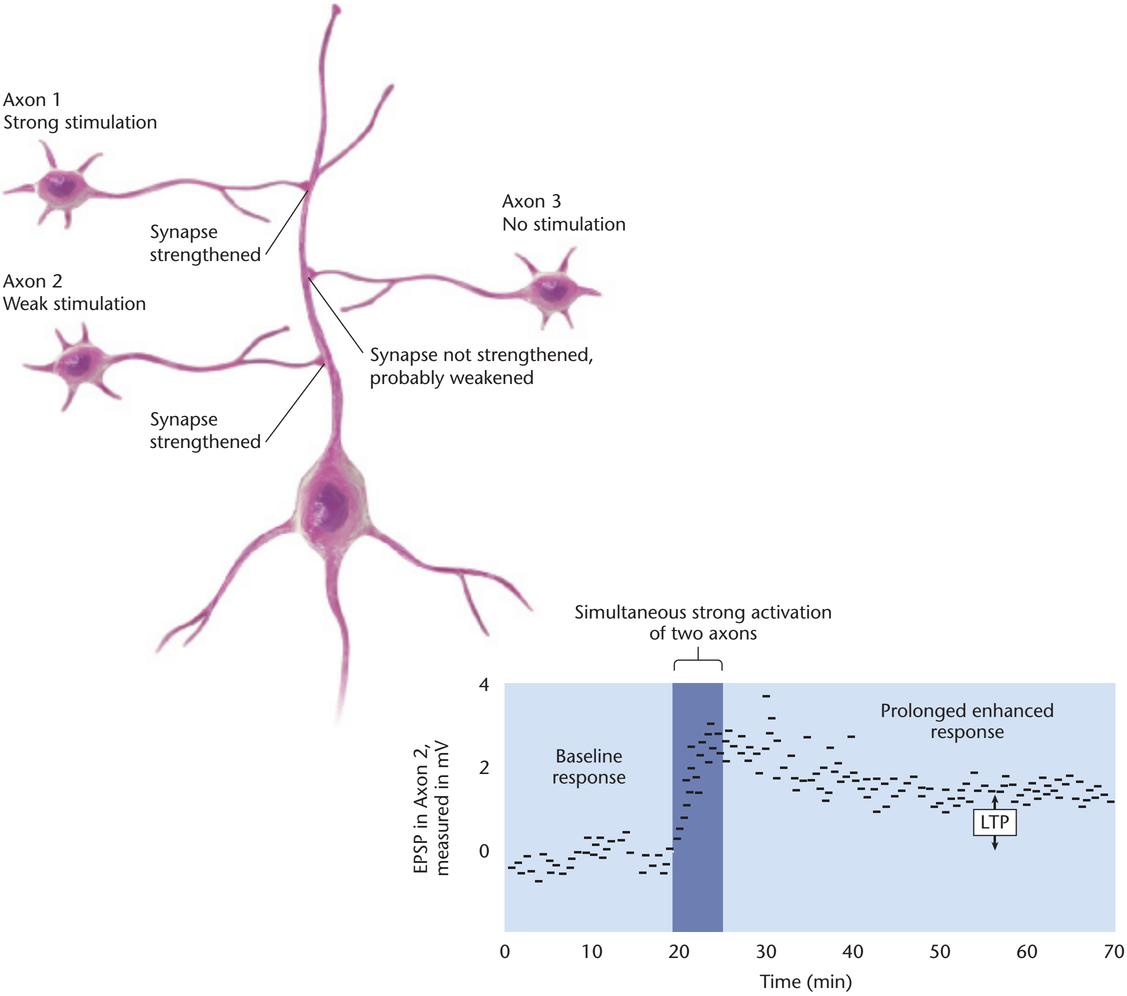
Long-term depression (LTD), a prolonged decrease in response at a synapse, occurs for axons that have been less active than others, such as axon 3 in Figure 12.17 (Collingridge et al., 2010). You can think of this as a compensatory process. As one synapse strengthens, another weakens (Royer and Paré, 2003). If learning produced only a strengthening of synapses, then every time you learned something, your brain would get more and more active, constantly burning more and more fuel.

Biochemical Mechanisms

Determining how LTP or LTD occurs has been a huge research challenge because each neuron has many tiny synapses, sometimes in the tens of thousands. Isolating the chemical changes at any synapse takes an enormous amount of creative, patient research. LTP occurs most readily in the hippocampus, and its mechanisms have been most extensively studied there.

Figure 12.18 Associativity in long-term potentiation

The response to axon 2 is initially weak. Briefly pairing it with rapid stimulation in axon 1 strongly depolarizes the dendrite. Afterward, the response to axon 2 (as well as axon 1) is enhanced.


Axon 1
Strong stimulation
Synapse strengthened
Axon 3
No stimulation
Axon 2
Weak stimulation
Synapse not strengthened, probably weakened
Synapse strengthened
Simultaneous strong activation of two axons
4
2
0
EPSP in Axon 2, measured in mV
Baseline response
Prolonged enhanced response
LTP
0
10
20
30
40
50
60
70
Time (min)

(**Source:** Collingridge, G. L., Peineau, S., Howland, J. G., & Wang, Y. T. (2010). Long-term depression in the CNS. *Nature Reviews Neuroscience*, *11*, 459–473.)

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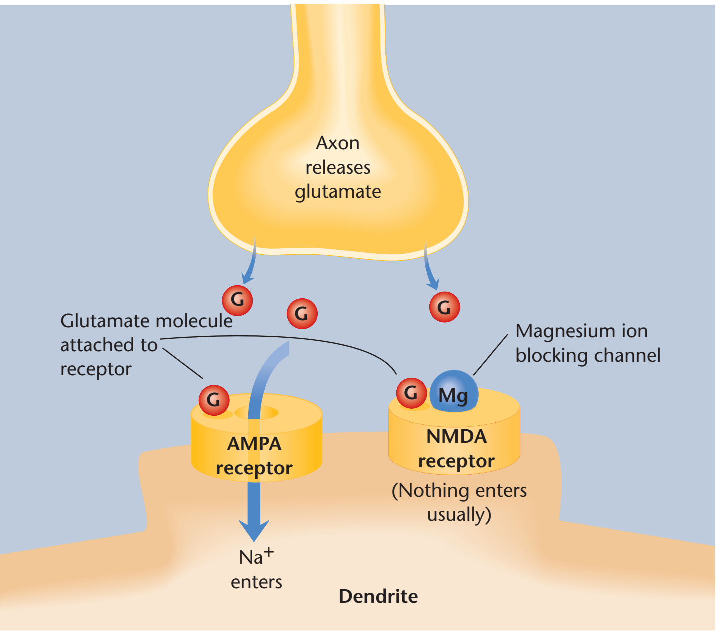
AMPA and NMDA Synapses

In some cases, LTP occurs at GABA synapses (Chiu et al., 2019; Nugent et al., 2007), but in most cases, it occurs at glutamate synapses. The brain has several types of receptors for glutamate, its most abundant transmitter. Neuroscientists identify types of dopamine receptors by number, such as D_1 and D_2, and GABA receptors by letter, such as $GABA_A$. They identify serotonin (5-hydroxytryptamine) synapses by both letter and number, such as $5HT_{2C}$. For glutamate, they named the receptors after drugs that stimulate them. Here we are interested in two types of glutamate receptors, called AMPA and NMDA. The **AMPA receptor** is excited by the neurotransmitter glutamate, but it can also respond to a drug called α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (mercifully abbreviated AMPA). The **NMDA receptor** is also excited by glutamate, but it can respond to N-methyl-D-aspartate (NMDA).

Figure 12.19 The AMPA and NMDA receptors before LTP

Glutamate attaches to both receptors. At the AMPA receptor, it opens a channel to let sodium ions enter. At the NMDA receptor, it opens the channel only when the magnesium ions dislodge.



Both are ionotropic receptors. That is, they respond to stimulation by opening a channel that lets ions enter the postsynaptic cell. The AMPA receptor is a typical ionotropic receptor that opens sodium channels. The NMDA receptor's response depends on the degree of polarization across the membrane. When the membrane is at its resting potential, the NMDA receptor's ion channel is usually blocked by magnesium ions. Magnesium ions, positively charged, are attracted to the negative charge inside the cells but do not fit through the NMDA channel. The NMDA channel permits ions to flow through it only if the magnesium leaves, and the surest way to detach the magnesium is to depolarize the membrane, decreasing the negative charge that attracts it (Figure 12.19).

Suppose an axon releases glutamate repeatedly. Better yet, let's activate two axons repeatedly, side by side on the same dendrite. Enough sodium ions enter through the AMPA channels to depolarize the dendrite, displacing the magnesium molecules and enabling the NMDA channel to open. At that point, both sodium and calcium enter through the NMDA channel (Figure 12.20).

The entry of calcium is the key to producing LTP. When calcium enters through the NMDA channel, it activates the protein αCaMKII[1] (Lisman et al., 2002; Otmakhov et al., 2004) that causes reactions leading to another protein, CREB.[1] (The footnote explains these abbreviations.) CREB enters the cell nucleus and regulates the expression of several genes. In some cases, the altered gene expression lasts long enough to account for long-term memory (Miller et al., 2010). Because αCaMKII remains at the stimulated synapse and does not diffuse elsewhere, it is responsible for the specificity aspect of LTP—the fact that only the activated synapses become strengthened (Lisman et al., 2012; Redondo and Morris, 2011; Wang et al., 2009).

When a neuron is potentiated, the action potentials that start in its axons back-propagate into the dendrites, which then release **BDNF**—brain-derived neurotrophic factor. The formation and maintenance of LTP depends on all these chemicals—αCaMKII, CREB, and BDNF (Kuczewski et al., 2008; Minichiello, 2009; Silva et al., 2009).

In some cases, LTP increases the later responsiveness of AMPA receptors (Lauterborn et al., 2016; Lisman et al., 2012). In other cases, it builds new dendrites and synapses that form a functional cluster with the dendrites already present (Hedrick et al., 2022). Figure 12.21 shows an example (Zhang et al., 2015).

Let's summarize: When glutamate massively stimulates AMPA receptors, the resulting depolarization enables glutamate to stimulate nearby NMDA receptors also. Stimulation of the NMDA receptors lets calcium enter the cell, where it sets into motion a series of changes that regulate gene expression to build new glutamate synapses or increase response to glutamate at existing AMPA receptors. After LTP occurs, NMDA receptors revert to their previous condition.

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[1] CaMKII = α-calcium-calmodulin-dependent protein kinase II. CREB = cyclic adenosine monophosphate responsive element-binding protein.

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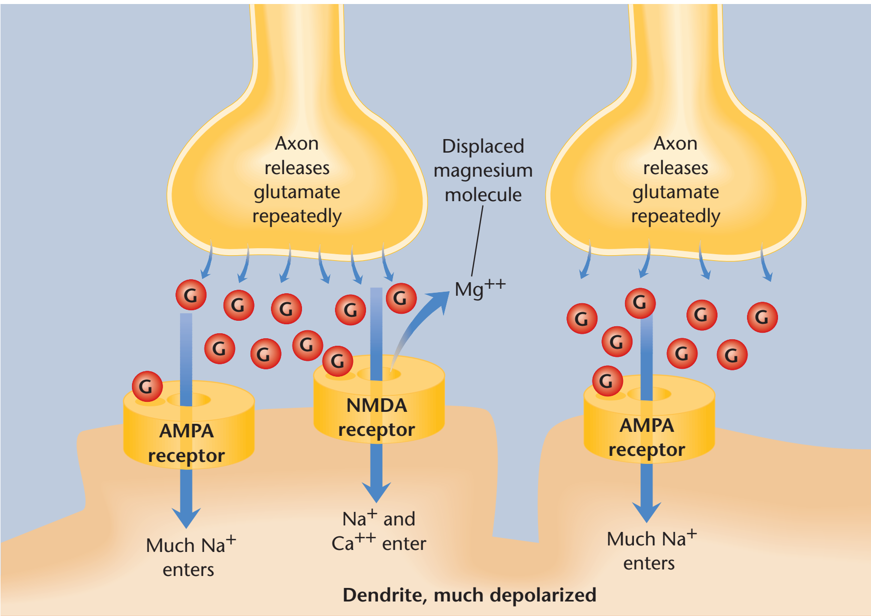
Figure 12.20 The AMPA and NMDA receptors during LTP

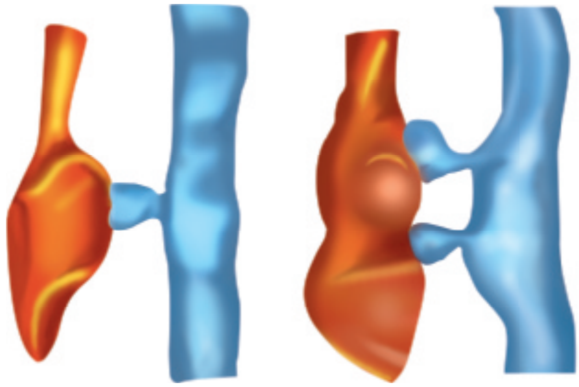
If AMPA receptors have been repeatedly stimulated, enough sodium enters to depolarize the dendrite's membrane. Doing so displaces the magnesium ions and enables glutamate to open the NMDA receptor, through which sodium and calcium enter.


Axon releases glutamate repeatedly
Displaced magnesium molecule
Axon releases glutamate repeatedly
Mg++
G
AMPA receptor
NMDA receptor
AMPA receptor
Much Na+ enters
Na+ and Ca++ enter
Much Na+ enters
Dendrite, much depolarized

Once LTP has been established, it no longer depends on NMDA synapses. Drugs that block NMDA synapses prevent the *establishment* of LTP, but they do not interfere with the *maintenance* of LTP that was already established (Gustafsson and Wigström, 1990; Uekita and Okaichi, 2005).

Figure 12.21 Added synapses as a result of LTP

These photos show part of one mouse dendrite before and three hours after the onset of LTP. The areas in blue indicate glutamate synapses.



(**Source:** From "Visualization of NMDA receptor-dependent AMPA receptor synaptic plasticity *in vivo*," by Y. Zhang, R. H. Cudmore, D.-T. Lin, D. J. Linden, and R. L. Huganir, 2015, *Nature Neuroscience*, *18*, 402–407.)

Presynaptic Changes

The changes just described occur in the postsynaptic neuron. Changes in the presynaptic neuron contribute also. Extensive stimulation of a postsynaptic cell causes it to release a **retrograde transmitter** such as nitric oxide (NO) that travels back to the presynaptic cell to decrease its threshold for producing action potentials (Ganguly et al., 2000), expand its axon (Routtenberg et al., 2000), and increase its release of neurotransmitter (Reid et al., 2004; Zakharenko et al., 2001). When both presynaptic and postsynaptic changes contribute to LTP, the result is greater precision and stability of learning (Costa et al., 2015).

Research on LTP shows us a mechanism whereby experience can alter the input–output properties of a neuron. Many studies have shown that LTP is important for learning and that interfering with LTP interferes with learning. However, it should be clear that understanding LTP is just one step toward understanding learning. Except for perhaps the simplest cases of classical conditioning, learning requires more than just increasing the response to a stimulus. Researchers will need to continue exploring how the wiring diagram makes possible all the complexities of a learned response.

Stop & Check

20. Before LTP, what is the effect of glutamate at the AMPA receptors? At the NMDA receptors?
21. During the formation of LTP, when a burst of intense stimulation releases much more glutamate than usual at two or more incoming axons, what is the effect of the glutamate at the AMPA receptors? At the NMDA receptors?
22. After the neuron has gone through LTP, what is now the effect of glutamate at the AMPA receptors? At the NMDA receptors?

See page 415 for the answer.

Improving Memory

Researchers study the biological mechanisms of memory for theoretical reasons but also in the hope of practical applications. Theoretically, a drug that enhanced LTP might improve memory. However, nearly all the products

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marketed so far to improve memory act as stimulants or by improving overall health.

Stimulant drugs such as caffeine, amphetamine, or methylphenidate (Ritalin) can aid memory when someone's arousal is low. Although buying amphetamine or methylphenidate without a prescription is illegal, many students have obtained the drugs and tried them at least once. The research suggests that the increased energy slightly improves some types of performance for average or below-average students, but it provides little or no benefit and possibly harm for better students (Ilieva et al., 2015; Smith and Farah, 2011). Modafinil, another stimulant drug, has shown only slight benefits (Roberts et al., 2020).

You may have heard claims that the herb *Ginkgo biloba* improves memory. Most of the research on *G. biloba* has been of low quality, and the results have been inconsistent (Yang et al., 2016). The benefits, if any, seem to be limited to people with Alzheimer's disease or similar conditions, and they develop only after long-term use (Stough and Pase, 2015).

Another herb, *Bacopa monnieri*, also known as water hyssop, has been used in India since the sixth century for several mental conditions. It works as an antioxidant and removes β-amyloids, and theoretically it seems a reasonable candidate for improving memory. The research is not extensive, but it suggests that *B. monnieri* may help some people's memory after prolonged use (Stough and Pase, 2015). Don't expect it to help for your test next week. Cocoa flavanols are chemicals found in cocoa, berries, grapes, apple, and tea, especially green tea. By dilating arteries, they improve blood flow to the brain and improve cognitive performance for many people (Gratton et al., 2020; Martín et al., 2020).

Several companies market over-the-counter supplements that claim to help brain functioning and memory. The Food and Drug Administration (FDA) does not regulate supplements, unless they make medical claims that go beyond the data or if they contain dangerous components, and the FDA does not always check the ingredients in a supplement. Many of the supplements marketed to aid brain functioning or memory have never been subjected to a placebo-controlled study, or if they were tested, it was only once in a small-scale study by the company itself. Ads can feature people who say that they thought the product benefited them, regardless of whether placebo-controlled studies show a significant benefit. Most cognitive supplements contain a mix of vitamins, minerals, and nutrients that are good for general health, even if they don't do much specifically for the brain, but some supplements contain drugs not approved by the FDA, drugs not listed on the label, or dangerously high levels of chemicals that are acceptable at lower doses (Cohen et al., 2021).

Another possibility, transcranial direct current stimulation, consists of applying a nonpainful 1 to 2 milliamp current to the scalp. The procedure has shown promising results for treating depression, chronic pain, Parkinson's disease, and other conditions, and possibly it helps people improve attention and memory. However, the procedure sometimes improves performance on one task while impairing another (Iuculano and Kadosh, 2013). It can also be dangerous if the electrodes are improperly placed or if the duration is too long (Maslen et al., 2014).

Behavioral methods to improve memory are still the best bet. If you want to remember something later, study it well now, rehearse it later, and periodically test yourself. Consistent physical exercise improves memory, as do good nutrition, adequate sleep, and stress management (Chapman et al., 2013; De Miguel et al., 2021; Smith and Farah, 2011).

Stop & Check

23. Why should you be unimpressed with the statement that a supplement has been "clinically tested"? Why should you be unimpressed by a testimonial that "this product works for me"?

See page 415 for the answer.

Module 12.3 | In Closing

The Physiology of Memory

Explaining memory in chemical terms underscores the idea of monism: Our experiences, our thoughts, and our memories are manifestations of chemical processes. All researchers manipulating chemicals at tiny synapses are in a real sense trying to help us understand human nature.

Summary

1. A Hebbian synapse becomes stronger when the presynaptic neuron successfully stimulates the postsynaptic neuron. **408**

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2. Habituation of the gill-withdrawal reflex in *Aplysia* depends on a mechanism that decreases the release of transmitter from a particular presynaptic neuron. **410**
3. Sensitization of the gill-withdrawal reflex in *Aplysia* occurs when serotonin blocks potassium channels in a presynaptic neuron and thereby prolongs the release of transmitter from that neuron. **410**
4. Long-term potentiation (LTP) is an enhancement of synaptic response because of a brief but intense series of stimuli delivered to a neuron, generally by two or more axons delivering simultaneous inputs. **410**
5. Long-term potentiation (LTP) has the properties of specificity, cooperativity, and associativity. **411**
6. If axons are active at a very slow rate, their synapses may undergo long-term depression (LTD). **411**
7. LTP in hippocampal neurons occurs as follows: Repeated glutamate excitation of AMPA receptors depolarizes the membrane. The depolarization removes magnesium ions that were blocking NMDA receptors. Glutamate can then excite the NMDA receptors, opening a channel for calcium ions to enter the neuron. **412**
8. When calcium enters through the NMDA channels, it sets in motion a series of events that increase receptor response or build additional synapses. **412**
9. Stimulant drugs sometimes improve memory or cognition when people lack arousal. Most supplements intended for cognitive enhancement have not been adequately tested. The best way to improve memory is to learn the material well and practice it. **413**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

AMPA receptor	**412**
associativity	**411**
BDNF	**412**
cooperativity	**411**
habituation	**410**
Hebbian synapse	**409**
long-term depression (LTD)	**411**
long-term potentiation (LTP)	**410**
NMDA receptor	**412**
retrograde transmitter	**413**
sensitization	**410**
specificity	**411**

Thought Questions

1. If a synapse developed LTP once, should it be easier or more difficult to get it to develop LTP again? Why?
2. The use of performance-enhancing drugs in sports is considered unethical and for most competitions illegal. Should we consider it unethical for people to use amphetamine or other performance-enhancing drugs when they are taking tests or otherwise competing academically?

Stop & Check Answers

18. In a Hebbian synapse, pairing the activity of a weaker (CS) axon with a stronger (UCS) axon produces an action potential, and in the process strengthens the response of the cell to the CS axon. On later trials, it will produce a bigger depolarization of the postsynaptic cell, which we can regard as a conditioned response.
19. Blocking potassium channels prolongs the action potential and therefore prolongs the release of neurotransmitters, producing an increased response.
20. Before LTP, glutamate stimulates AMPA receptors but usually not the NMDA receptors, because magnesium blocks them.
21. The massive glutamate input stimulates the AMPA receptors enough to depolarize the dendrite and enable glutamate to excite the NMDA receptors.
22. After LTP has been established, glutamate stimulates the AMPA receptors more than before, mainly because of an increased number of AMPA receptors. At the NMDA receptors, it is again usually ineffective.
23. Being clinically tested says nothing about the results of the test. A testimonial is no substitute for a double-blind placebo-controlled experiment.

Module 12.3 | End-of-Module Quiz

1. What is true about a Hebbian synapse?
   - **a.** It strengthens as a result of experience.
   - **b.** It can be either excitatory or inhibitory, depending on the activity of nearby synapses.
   - **c.** It responds to more than one neurotransmitter.
   - **d.** It can send messages between cells in either direction.

2. Cells that fire together wire together, but only if which of the following?
   - **a.** The cells are close together.
   - **b.** Both cells release the same neurotransmitter.

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c. The cells release different neurotransmitters.
d. At least one of the cells releases serotonin.

3. Why is *Aplysia* an appealing animal for studies of the physiology of learning?

a. It learns rapidly but also forgets rapidly.
b. The neurons are the same from one individual to another.
c. Its axon is thicker than that of mammals and therefore easier to study.
d. It has only one excitatory neurotransmitter and one inhibitory neurotransmitter.

4. What causes habituation in *Aplysia*?

a. Fatigue of the muscles
b. Decreased response by the sense organs
c. Decreased hormonal secretions
d. A change at a synapse

5. What is meant by the "associativity" of LTP?

a. Changes occur in both neurons and glia cells.
b. Habituation of one synapse causes sensitization of another one.
c. Pairing two stimuli increases responsiveness to the weak one.
d. Strengthening one synapse strengthens many others also.

6. How do AMPA and NMDA synapses differ?

a. They respond to different neurotransmitters.
b. One is excitatory and the other is inhibitory.
c. They respond differently to certain drugs.
d. They occur in different animal species.

7. Why are NMDA receptors usually unresponsive?

a. They respond to an uncommon neurotransmitter.
b. They have a long refractory period.
c. Magnesium ions block their channel.
d. Calcium ions block their channel.

8. Which ion enters through an NMDA channel when the synapse is stimulated?

a. Calcium
b. Magnesium
c. Chloride
d. Lithium

9. In the United States, is it possible to market a supplement that produces only placebo effects?

a. No, the FDA would prevent it.
b. Yes, if the advertisements do not make unverified claims.
c. Yes, if it has no side effects.
d. Yes, regardless of anything.

Answers: 1a, 2a, 3b, 4d, 5c, 6c, 7c, 8a, 9b.

Module 12.4

Intelligence

Intelligence, a difficult concept to define, includes learning, memory, reasoning, and problem solving. One of the first discoveries from psychological research was Charles Spearman's (1904) report that almost any measure of cognitive performance correlates positively with almost any other. That is, most people who are above average on any cognitive skill are above average on most of the others also. Many psychologists have therefore assumed that all the skills share a single underlying factor of general intelligence, known as ***g***. However, the fact that skills correlate does not necessarily mean that they measure the same thing. The size of any brain area correlates positively with the size of any other brain area, just because health, nutrition, and other factors that support the growth of one area also support the growth of others. The skills dependent on one brain area could correlate with those of another area even if they do not rely on an underlying general ability. We can find it convenient to talk about general intelligence, just as we talk about general athletic ability, but we also know that people can be intelligent in one way and not so much in another, just as people can excel in one athletic skill and not another.

Genetics and Intelligence

As with almost any psychological variable, variations in intelligence reflect contributions from both genetic and environmental influences. Evidence for a genetic effect includes the observation that monozygotic twins resemble each other more strongly than do dizygotic twins on tests of overall intelligence, specific cognitive abilities, and brain volume (Bishop et al., 2003; Haworth et al., 2010; McGue and Bouchard, 1998; Posthuma et al., 2002). Monozygotic twins resemble each other even if they are reared separately (Bouchard and McGue, 1981; Farber, 1981). Still, much else can modify intelligence, including effects of health, diet, education, and exposure to air pollution.

Heritability increases as people grow older, presumably because high-performing people gravitate toward educational opportunities and activities that facilitate and magnify their genetic predispositions (Haworth et al., 2010; Lyons et al., 2009; Tucker-Drob and Bates, 2016). Scores for monozygotic twins become more and more alike. Also, as adopted children grow older, the correlation of their test scores with their adoptive relatives decreases somewhat, while the correlation with their biological parents increases (Loehlin et al., 1989; Plomin et al., 1997; Segal et al., 2012).

Many genes known to be important for intelligence are described as "intolerant of variation" (M. R. Johnson et al., 2016). That is, they are the same in almost everyone, and mutations in them lead to intellectual disability (Ganna et al., 2016; Gilissen et al., 2014; Lelieveld et al., 2016). For people within the normal range of intelligence, researchers have identified more than a thousand gene variations with small but measurable correlations with intelligence (Savage et al., 2018). However, correlation is not the same as causation. For example, any gene that is more common in southeast Asia than in other parts of the world would correlate with eating more rice. Any gene that happens to be common in Norway would correlate with speaking Norwegian. If a gene correlates with intellectual function, we need research to find out why.

Stop & Check

24. What evidence supports the conclusion that genetic variation contributes to variations in human intelligence?

See page 421 for the answer.

Brain Size and Intelligence

People sometimes use the term *brainy* to mean intelligent. We assume that bigger brains are better, but it is not that simple.

In the 1800s and early 1900s, members of several societies of successful and famous men—yes, all men—agreed to donate their brains after death for research into the causes of their success. No conclusion resulted. The brains of the eminent people varied considerably, as did those of less eminent people (Burrell, 2004). Becoming eminent depends on opportunity, luck, effort, and so much else. Still, the idea lingers: Even if brain size or anatomy isn't strongly related to intelligence, shouldn't it have *some* relationship? Would we expect the correlation to be *exactly* zero?

Comparing Species

All mammalian brains have a similar organization, but they differ greatly in size. Does a larger brain mean greater intelligence? Long ago, Bernhard Rensch (1964) demonstrated that within a family of animals, the larger species, which have larger brains, learn faster and remember better than smaller species. Larger rodents do better than smaller rodents, and larger species in the chicken family do better than smaller ones. However, this trend does not hold when we compare species from separate families. Comparing animals from separate families is problematic. We have some vague ideas about the intelligence of animals—chimpanzees are smarter than worms, for sure—but if we try to get precise, the problems are serious (Macphail, 1985). Tasks that are appropriate for a dog are not equally appropriate for a zebra or a porcupine.

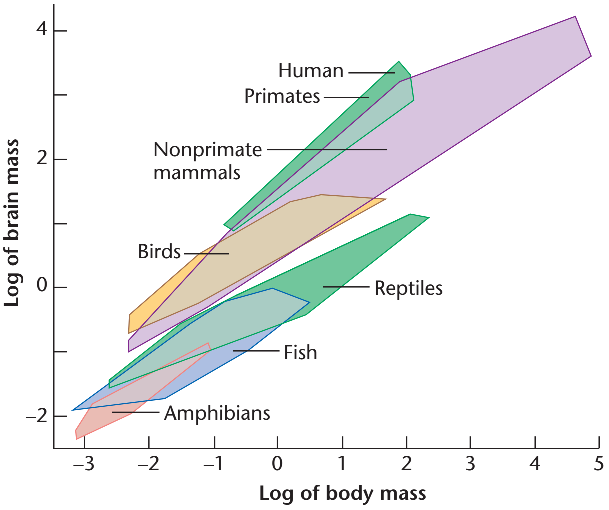
We humans like to think of ourselves as the most intelligent animals—after all, we defined what intelligence means—but whales and elephants have larger brains than we do. Might intelligence depend on brain-to-body ratio? Figure 12.22 illustrates the relationship between logarithm of body mass and logarithm of brain mass for various vertebrates (Jerison, 1985). Note that the species we regard as most intelligent—such as, ahem, ourselves—have larger brains in proportion to body size than do the species we consider less impressive, such as frogs.

However, brain-to-body ratio has limitations also: Chihuahuas have the highest brain-to-body ratio of all dog breeds, not because they were bred for intelligence but because they were bred for small bodies (Deacon, 1997). Squirrel monkeys and marmosets have a higher brain-to-body ratio than humans. (And because of the increasing prevalence of human obesity, our brain-to-body ratio is declining!) The elephant-nose fish, which you might keep in an aquarium, has a 3 percent brain-to-body ratio compared to 2 percent for humans (Nilsson, 1999). The tiniest ants have a 15 percent brain-to-body ratio (Seid et al., 2011). Neither total brain mass nor brain-to-body ratio puts humans in first place.

However, humans do lead in one aspect, by a considerable margin: total number of neurons. Although whales and elephants have larger brains than humans, their neurons are larger and more spread out. Although marmosets have a greater brain-to-body ratio than humans, marmosets' bodies are smaller, and therefore they have fewer neurons. Suzana Herculano-Houzel (2011a) demonstrated that humans have the largest number of brain neurons (Figure 12.23). In most animal families, the species with larger brains also have larger neurons, so that the ones with larger brains have only moderately larger numbers of neurons. Raccoons and

Figure 12.22 Relationship of brain mass to body mass across species

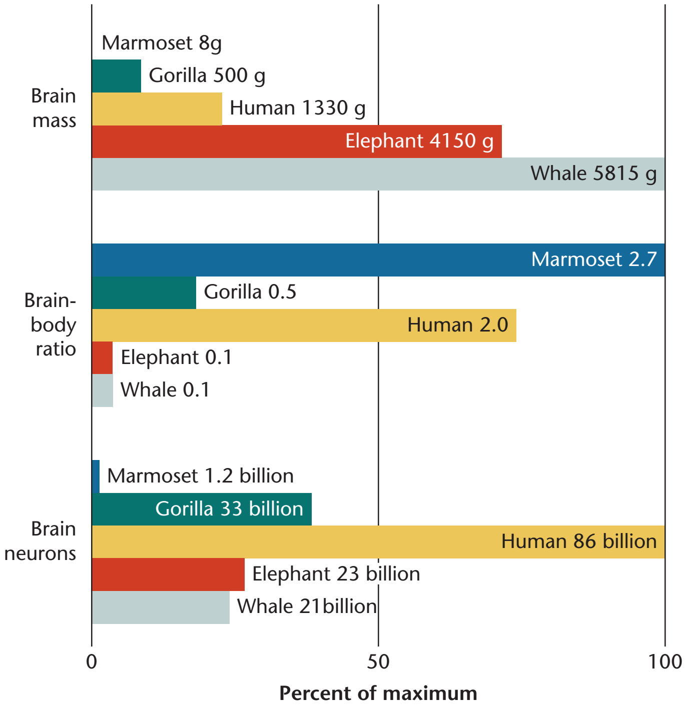
Each species is one point within one of the polygons. In general, log of body mass is a good predictor of log of brain mass. Primates and especially humans have a large brain mass in proportion to body mass.



(**Source:** Adapted from Jerison, 1985)

Figure 12.23 Three ways of comparing brains across species

Humans do not have the largest brain mass or the largest brain-to-body ratio, but we do have the largest number of brain neurons.



(**Source:** Based on the best available estimates, from Herculano-Houzel, 2011a.)

bears are distantly related, but raccoons have smaller, more densely packed neurons (Jardim-Messeder et al., 2017). In primates, however, the species with larger brains have the same size neurons as those with smaller brains. As a result, humans' neuron total is much elevated (Herculano-Houzel, 2012).

Thus, total number of neurons may be a reasonable correlate of intelligence (to the extent that we regard intelligence as a reasonable concept when comparing species). Further support comes from the observation that birds in the crow and parrot families, which have demonstrated impressive problem-solving skills (Wright et al., 2017), have as many neurons as a small monkey, because crows' and parrots' neurons are so tightly packed (Dicke and Roth, 2016; Olkowicz et al., 2016). Intelligence also depends on much else (Santarnecchi et al., 2014). What matters is what the neurons do, not just how many there are.

Stop & Check

25. Why are both brain size and brain-to-body ratio unsatisfactory ways of estimating animal intelligence?

See page 421 for the answer.

Human Data

For many years, studies of human brain size and intelligence found correlations near zero. A low correlation between variables can mean that they are unrelated, but it can also mean that one or both variables were measured poorly. Early studies measured skull size to estimate brain size, but skull size and brain size do not match well. (Some people are thick skulled!) Today, measurements based on MRI find a low positive correlation between brain size and IQ score (Pietschnig et al., 2015). The best way to conduct a study is to compare people within a family. With that design, researchers found a correlation of 0.18 with one population sample and 0.19 with another (Lee et al., 2019). A study with a larger sample (more than 13,000 people), but not limited to people within a family, also found a 0.19 correlation (Nave et al., 2019). That represents a modest relationship.

Intelligence scores correlate with total brain volume, surface area of the cortex, several white-matter tracts, and the volume of several subcortical areas (Chen et al., 2020; Jung et al., 2020; Tadayon et al., 2020). However, although the correlations are interesting, they are far too low to make useful predictions about an individual (Hilger et al., 2020). If you want to identify smart people, attend to their actions, not their brain measurements, just as you would identify good athletes by their performance and not their muscle size.

A theoretical problem arises: Men on average have about 10 percent larger brains than women but equal IQ scores (Burgaleta et al., 2012; Gilmore et al., 2007; Willerman et al., 1991; Witelson et al., 2006). Also, contrary to what many people believe, girls' grades in nearly all mathematics courses are at least as good as boys' grades from elementary school through college (Hyde et al., 2008; Spelke, 2005).

How can we explain why men and women are equal in intellect, although men have a larger brain? One possibility is that females may have smaller neurons, and therefore the same number of neurons and synapses packed into a smaller volume. So far, no one has checked that possibility. Also, male and female brains are organized somewhat differently. On average, some brain areas form a larger percentage of the male brain and others form a larger percentage of the female brain (Del Mauro et al., 2022). Some connections are stronger in males and others in females, again on average, including stronger connections between the two hemispheres in females (Gong et al., 2011; Ritchie et al., 2018; Tunc et al., 2016). Female brains may be organized somewhat differently to produce the same intellectual abilities as the somewhat larger male brains (Grabowska, 2017).

The apparent link between intelligence and brain size or the number of neurons can take us only so far. A good understanding of brain processes or psychological processes requires analysis of the more detailed ways in which each brain area contributes to specific aspects of behavior and experience.

Stop & Check

26. Why do recent studies show a stronger relationship between brain size and IQ than older studies did?

See page 421 for the answer.

© Suzana Herculano-Houzel

Suzana Herculano-Houzel (b. 1972)

The evolution of the human brain, with its high metabolic cost imposed by its large number of neurons, may thus only have been possible because of the use of tools and later fire to break down and cook foods, enabling individuals to ingest in very little time the entire caloric requirement for the day, and thereby freeing time to use the added neurons to their competitive advantage. (Herculano-Houzel, 2012, p. 10667, modified by personal message)

Brain Evolution

Except for the specializations related to language, human brains are organized the same way as those of other mammals. We have the same types of neurons, the same neurotransmitters, the same types of synapses, approximately the same ratio of neurons to glia cells, and so forth (Harris and Shepherd, 2015; Herculano-Houzel, 2012). Just a few genetic differences between humans and other primates are enough to cause more rapid and more prolonged production of neurons during embryological development, leading to a larger cerebral cortex and a larger number of neurons (Bakken et al., 2016; Herculano-Houzel, 2012; Pennisi, 2015). Expressing one of those genes in a marmoset monkey caused expansion of the cortex and extra folds in the surface (Heide et al., 2020). A few other genetic changes altered synaptic transmission in a few brain areas (Sousa et al., 2017).

How did we manage to evolve such a large brain, whereas other species did not? The brain is a metabolically expensive organ. The human brain constitutes only 2 percent of the body's mass, but it consumes 20 percent of its fuel. When researchers selectively bred guppies (small fish) for larger brains, they found that these guppies had less energy available for other organs, including the reproductive system, and the guppies produced fewer than average offspring (Kotrschal et al., 2013). In a world where most baby fish get eaten, sacrificing babies for big brains would be a bad bet, evolutionarily.

For our remote ancestors to evolve such large brains, they needed to get a great deal of nutrition, but they also needed to reduce the energy spent on other functions. Our upright walking is efficient and saves energy (Pontzer et al., 2016). At some point in our early evolutionary history, our ancestors learned to cook their food, making it easier to digest. Thus, they could evolve a smaller digestive tract that used less energy. Also, they hunted in groups, bringing back more food than one person alone could find, and they learned to catch fish and harvest shellfish, rich in nutrition. Furthermore, humans differ from chimpanzees in two genes responsible for glucose transport: We have more of the protein that transports glucose into the brain, and less of the protein that transports it into the muscles (Fedrigo et al., 2011). We devote more energy to our brains and less to physical strength. Hunting in groups and making tools for weapons made it possible to get food without such big muscles.

Our remote ancestors also decreased the energy required for reproduction. Compared to most species, people bear fewer offspring over a lifetime but devote enough care to increase the probability of survival. A further essential is cooperation. Even young children spontaneously learn to take turns, unlike chimpanzees (Melis et al., 2016). Persisting family groups and food sharing within a community made it easier to raise an infant (Fletcher et al., 2015; Isler and van Schaik, 2009).

Stop & Check

27. Why were our ancient ancestors able to evolve larger numbers of neurons than other species?

See page 421 for the answer.

Module 12.4 | In Closing

Why Are We So Intelligent?

Humans are like other mammals in many ways, but we are also unusual. We cook our food, we share food, we cooperate for raising children, and we have big brains. All those adaptations had to happen together. The big brains were important for cooking, sharing, and raising children. Cooking, sharing, and cooperatively raising children were essential for evolving big brains. The humans of today are the product of an amazing and very special evolutionary history.

Summary

1. Genetic differences contribute to differences in intelligence. Although some cases of intellectual impairment can be attributed to a genetic variant, no single gene produces a big effect for people within the normal range. **417**
2. Although several other species have larger brains or a larger brain-to-body ratio, the human brain has more neurons. **418**
3. Among humans, brain size has a small correlation (about .19) with measurements of intelligence. **419**
4. Men and women have equal intelligence, although men have a larger brain. **419**
5. Ancient humans were able to evolve a larger brain and more neurons because they needed less energy than other species for locomotion, digestion, and reproduction. **420**

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Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

Thought Question

1. If we discover that another planet has intelligent life, what kind of message could we send that they might understand?

Stop & Check Answers

24. The evidence is based largely on comparisons of monozygotic and dizygotic twins. Also, genetic mutations can produce intellectual disabilities.

25. If we consider ourselves to be the most intelligent species, we are confronted with the fact that we have neither the largest brains nor the highest brain-to-body ratios. Total neuron number is a more promising correlate of intelligence.

26. The use of MRI greatly improves the measurement of brain size, in comparison to measurements based on the skull.

27. Because of cooking, cooperative breeding, and upright locomotion, they were able to decrease the energy necessary for other organs and functions.

Module 12.4 | End-of-Module Quiz

1. What is meant by the *g* factor of intelligence?
   - **a.** Genetic
   - **b.** Generation
   - **c.** General
   - **d.** Good

2. The evidence for a genetic contribution to intelligence comes mainly from what type of research?
   - **a.** Measurements of brain anatomy
   - **b.** Changes over generations
   - **c.** Comparisons of cultures
   - **d.** Comparison of twins

3. Human brains exceed those of all other species in what regard?
   - **a.** Number of neurons
   - **b.** Total brain volume
   - **c.** Brain to body ratio
   - **d.** Variety of neurotransmitters

4. Why would it be a mistake to measure people's intelligence by measuring their brains?
   - **a.** It would be illegal and unethical.
   - **b.** The correlation between brain size and intelligence is low.
   - **c.** Measuring brain size is complicated and expensive.
   - **d.** Brain size varies from one time to another.

5. When researchers selectively bred guppies for large brains, which of these occurred?
   - **a.** The guppies developed richer social behaviors.
   - **b.** The guppies decreased their appetite.
   - **c.** The guppies decreased their reproduction.
   - **d.** The guppies increased their activity levels.

6. Theorists believe that early humans were able to evolve greater intelligence because of an improvement in what?
   - **a.** Exercise
   - **b.** Nutrition
   - **c.** Sexual activity
   - **d.** Body temperature

Answers: 1c, 2d, 3a, 4b, 5c, 6b.

Suggestion for Further Reading

Corkin, S. (2013). *Permanent present tense.* (Basic Books). Thorough account of the life of amnesia patient Henry Molaison and psychologists' research on his memory.

McPherson, S. E., and Della Sala, S. (2019). *Cases of amnesia*. (Routledge). Discussion of many types of amnesia following brain damage, and what they tell us about memory.

Chapter 13

John, Jenny, Max, Tony meeting on Mon. 10 am.
CHECK A/R BALANCE
Money in bank!
CALL HELEN IMPORTANT!!!
Check legal dept about new contract
Get new pass from security.
School Play. Wed 8pm
8624
SHIP CD's TO CORPORATE
USER ID: 2bx 1927 #1 #2
Check contract expiry.
Stationary Supplies Printer Ink Staples Pins Pens.
PICK UP DRY CLEANING
Call PLUMBER
Check deadline for South American project.
EMAIL JEFF RE CREDIT REPORT
Cancel hairdresser on Wed.
Renew subscripti
STAFF MEETING 10:30AM
RETURN DVD TO JOE
CONF. CALL 9AM
Video for Ann.
CALL FINANCE DEPT
Strategy Meeting Tues 1.00
ANNIVERSARY 4/16
Make 2nd set of keys.
GET MARKETING REPORT
Check Email for Doug.
Talk to John about network issues.
Call dentist early!!
BOOK FLIGHT TO LONDON SEPT.
Check with Samantha about ski trip.
Printer won't work on email docs.
Check numbers on quarterly report. and recheck!!
— MILK — EGGS — BREAD — DOG FOOD — TISSUES
KEYCODE 4576
FLU SHOT ON TUES.
SALES PROGRAM FOR TOM
CALL SITTER FOR FRIDAY NIGHT
FINISH
Don't
Password
COLLECT $$$ FROM FUND RAISER
CALL SEATTLE OFFICE

People have devised many ways to communicate.

(Helen King/Corbis/Getty Images)

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Cognitive Functions

Chapter Outline

Module 13.1

Lateralization and Language

The Left and Right Hemispheres
Visual and Auditory Connections to the Hemispheres
The Corpus Callosum and the Split-Brain Operation
Language Precursors in Other Species
How Did Language Evolve?
Brain Damage and Language
Dyslexia
In Closing: Language and the Brain

Module 13.2

Consciousness

The Mind–Brain Relationship
Consciousness of a Stimulus
Inferring Overall Consciousness or Unconsciousness
Attention
In Closing: Being Conscious of Consciousness

Module 13.3

Making Decisions and Social Neuroscience

Decisions
The Biology of Love
Social Interactions
In Closing: Biology of Decisions and Social Behavior

Learning Objectives

After studying this chapter, you should be able to:

1. Contrast the functions of the left and right hemispheres.
2. Describe the visual and auditory connections to the hemispheres.
3. Describe the results of split-brain surgery.
4. Describe the attempts to teach language to nonhumans.
5. Explain why increased intelligence does not explain language evolution.
6. Evaluate the concept of a sensitive period for language development.
7. Describe and contrast two categories of aphasia.
8. Discuss what is known about bilingualism.
9. Describe research on dyslexia.
10. Explain why nearly all neuroscientists and philosophers favor some version of monism with regard to the mind–brain relationship, and discuss the identity position.
11. Describe the brain activities that differ between conscious and unconscious processing of a stimulus, and the research supporting these conclusions.
12. Discuss and evaluate proposed methods of determining whether an unresponsive person might be conscious.
13. Describe the brain mechanisms of attention.
14. Describe research on the brain mechanisms of perceptual decisions.
15. Describe research on the brain mechanisms of value decisions.
16. List key findings about biological influences on social behavior.

All good research depends on accurate measurement. Language, attention, thinking, and decision making are hard to measure, and therefore hard to study. Nevertheless, many of the results are fascinating. After damage to the corpus callosum, people at least briefly act as if they have two fields of awareness—"separate minds," you might say. With damage to certain areas of the left hemisphere, people lose their language abilities while retaining other abilities. Researchers can identify brain reactions that differ depending on whether someone is or is not conscious of a stimulus. Certain types of brain damage interfere with making good decisions or empathizing with others. Progress is occurring in areas previously regarded as unapproachable.

Module 13.1

Lateralization and Language

Learning Objectives

After studying this module, you should be able to:

1. Contrast the functions of the left and right hemispheres.
2. Describe the visual and auditory connections to the hemispheres.
3. Describe the results of split-brain surgery.
4. Describe the attempts to teach language to nonhumans.
5. Explain why increased intelligence does not explain language evolution.
6. Evaluate the concept of a sensitive period for language development.
7. Describe and contrast two categories of aphasia.
8. Discuss what is known about bilingualism.
9. Describe research on dyslexia.

Symmetry is common in nature. The sun, stars, and planets are nearly symmetrical, as are most animals and plants. The human brain is almost symmetrical, but not quite. This module explores the distinctions between hemispheres, and then progresses to what we know about the biology of language.

The Left and Right Hemispheres

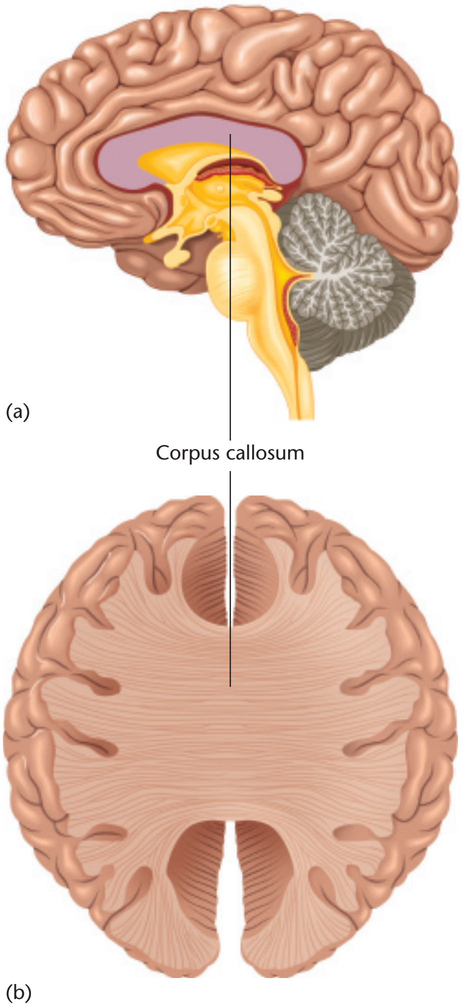
The left hemisphere of the cerebral cortex connects to skin receptors and muscles mainly on the right side of the body, and the right hemisphere connects to skin receptors and muscles mainly on the left side. The exception is that both hemispheres control the trunk muscles and facial muscles. The left hemisphere sees the right half of the visual field, and the right hemisphere sees the left half of the visual field. Each hemisphere gets auditory information from both ears but slightly stronger information from the contralateral ear. *Why* did brains evolve so that each hemisphere controls the contralateral side of the body? No one knows. Taste and smell, however, are uncrossed. Each hemisphere gets taste information from both sides of the tongue (Stevenson et al., 2012) and smell information from the nostril on its own side (Herz et al., 1999; Homewood and Stevenson, 2001).

According to fMRI data and other methods, the left hemisphere is dominant for speech production in more than 95 percent of right-handers and nearly 80 percent of left-handers (McKeever et al., 1995). Some strongly left-handed people have right-hemisphere dominance for speech, but most left-handers have either left-hemisphere control or a mixture of left- and right-hemisphere control (Flowers and Hudson, 2013). Although the right hemisphere does not produce speech, it understands it (Huth et al., 2016). The right hemisphere has other functions, as we shall see later. Division of labor between the two hemispheres is called **lateralization**.

The left and right hemispheres exchange information through sets of axons called the **corpus callosum**, the anterior commissure, the hippocampal commissure, and a couple of other small commissures (Figure 13.1; also Figures 3.10 and 3.13). The corpus callosum and other connections enable each hemisphere to process information from both sides and coordinate movement on both sides. Only after damage to the corpus callosum or to one hemisphere do we see clear evidence of lateralization.

Figure 13.1 Two views of the corpus callosum

The corpus callosum is a large set of axons conveying information between the two hemispheres. **(a)** A sagittal section through the human brain. **(b)** A dissection (viewed from above) in which gray matter has been removed to expose the corpus callosum.



Anatomical Differences between the Hemispheres

Norman Geschwind and Walter Levitsky (1968) found that one section of the temporal cortex, the **planum temporale** (PLAY-num tem-poh-RAH-lee), is larger in the left hemisphere for 65 percent of people (Figure 13.2). The planum temporale is also larger on the left side in most infants as well (Hervé et al., 2013; Witelson and Pallie, 1973). Even 2-month-old children activate the left hemisphere more than the right when they listen to speech, and not when they listen to music (Dehaene-Lambertz et al., 2010).

Young children activate the right hemisphere during speech more than adults do. As they grow older, most of them gradually suppress the right hemisphere during speech and emphasize the left hemisphere (Olulade et al., 2020). In rare cases, a child does not develop a corpus callosum. In those cases, both hemispheres remain active during speech throughout life (Hinkley et al., 2016). In short, the left hemisphere is predisposed to dominate for speech, and ordinarily it gradually suppresses the speech capacity of the right hemisphere.

Smaller differences are found between left and right hemispheres of chimpanzees, bonobos, and gorillas (Hopkins, 2006). Evidently, the specialization we see in the human brain built upon specializations present in our apelike ancestors of long ago.

Stop & Check

1. Most adults with left-hemisphere damage lose their speech, with little recovery. Young children with similar damage recover much better. Why?

See page 439 for the answer.

Visual and Auditory Connections to the Hemispheres

Let's start with the sensory connections to the brain. The hemispheres connect to the eyes such that each hemisphere sees the opposite half of the visual world. In rabbits and other species with eyes far to the side of the head, the left eye connects to the right hemisphere, and the right eye connects to the left. Human eyes are not connected to the brain in this way. Both of your eyes face forward and see both halves of the world.

In humans, each hemisphere is connected to half of each eye, as Figure 13.3 illustrates. Light from the right half of the **visual field** (what one sees) strikes the left half of each retina, which connects to the left hemisphere, enabling it to see the right visual field. Light from the left visual field strikes the right half of each retina, which connects to the right hemisphere. A vertical strip down the center of each retina, covering about 5 degrees of visual arc, connects to both hemispheres (Innocenti, 1980; Lavidor and Walsh, 2004). In Figure 13.3, note how approximately half of the axons from each eye cross to the opposite side of the brain at the **optic chiasm** (literally, the "optic cross").

Right visual field ⇒ left half of each retina ⇒ left hemisphere
Left visual field ⇒ right half of each retina ⇒ right hemisphere

The auditory system is organized differently. Each ear sends some of the information to both sides of the brain, because any brain area that contributes to localizing sounds must compare input from both ears. Nevertheless, each hemisphere pays more attention to the ear on the opposite side (Hugdahl, 1996).

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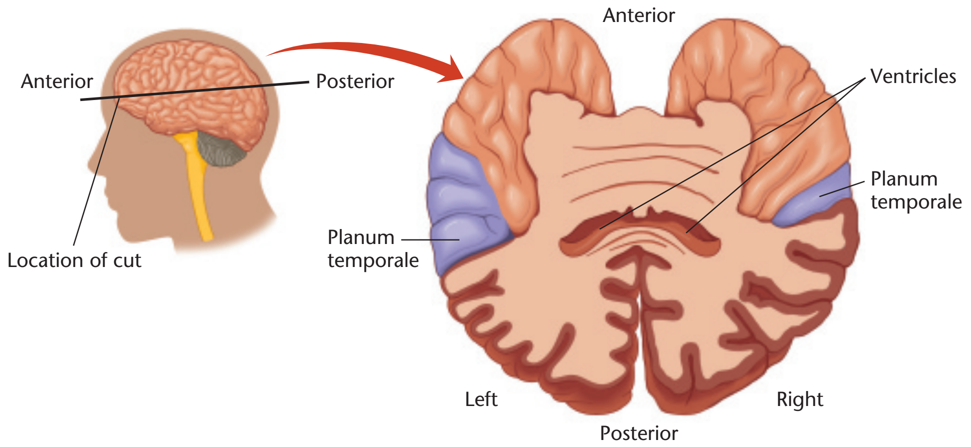
Figure 13.2 Horizontal section through a human brain

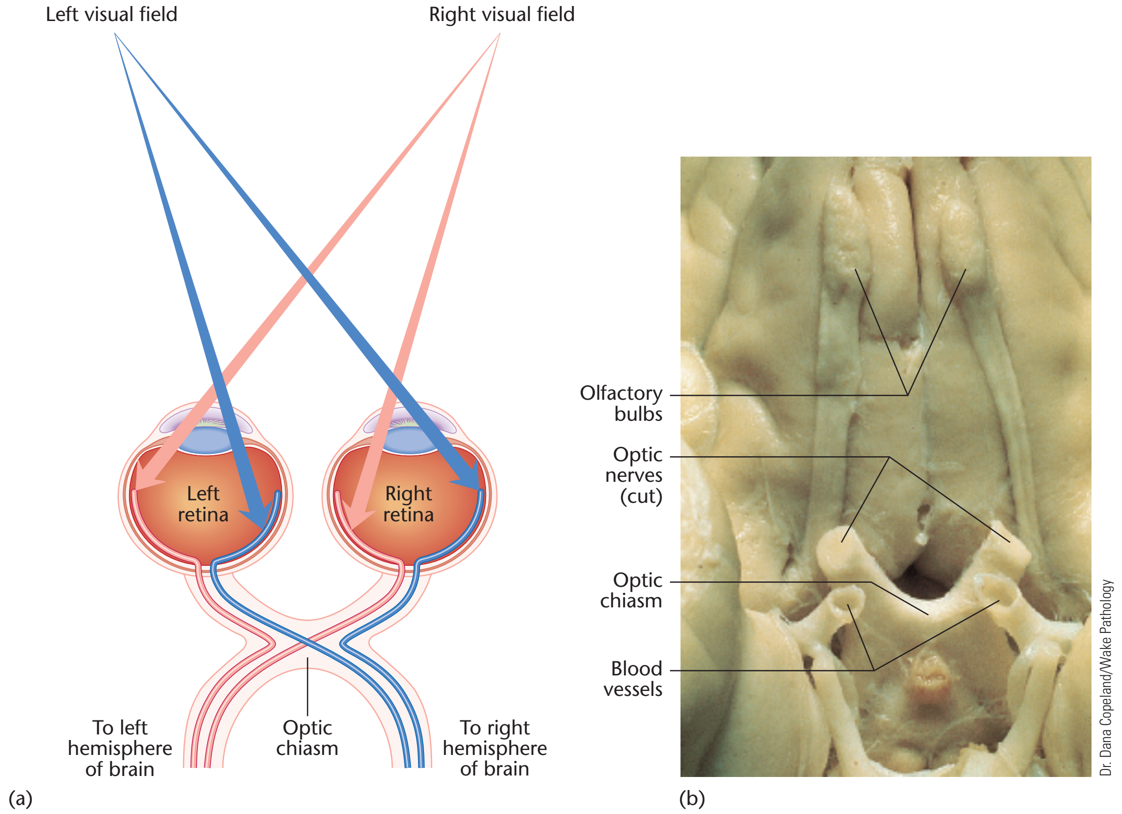
This cut, just above the surface of the temporal lobe, shows the planum temporale, an area critical for speech comprehension. It is larger in the left hemisphere than in the right hemisphere.


Anterior
Posterior
Location of cut
Anterior
Ventricles
Planum temporale
Planum temporale
Left
Right
Posterior

(**Source:** From "Human brain: Left-right asymmetries in temporal speech region," by N. Geschwind and W. Levitsky, 1968, *Science, 161,* 186–187. Copyright © 1968 by AAAS and N. Geschwind. Reprinted with permission.)

Figure 13.3 Connections from the eyes to the human brain

(a) The left hemisphere connects to the left half of each retina and thus gets visual input from the right half of the world. The opposite is true of the right hemisphere. **(b)** At the optic chiasm, axons from the right half of the left retina cross to the right hemisphere, and axons from the left half of the right retina cross to the left hemisphere.


Left visual field
Right visual field
Left retina
Right retina
To left hemisphere of brain
Optic chiasm
To right hemisphere of brain
(a)
Olfactory bulbs
Optic nerves (cut)
Optic chiasm
Blood vessels
(b)
Dr. Dana Copeland/Wake Pathology

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Stop & Check

2. The left hemisphere of the brain is connected to the right eye in guinea pigs. In humans, the left hemisphere is connected to the left half of each retina. Explain the reason for this species difference.
3. In humans, the left half of each retina receives visual information from which side of the world and sends its output to which hemisphere?

See page 439 for the answer.

The Corpus Callosum and the Split-Brain Operation

Epilepsy is a condition characterized by repeated episodes of excessive synchronized neural activity. More than 90 percent of patients with epilepsy respond well to anti-epileptic drugs, but if someone continues having frequent, severe seizures despite medication, physicians consider surgically removing the *focus,* the point in the brain where the seizures begin. The location of the focus varies from one person to another.

Removing the focus is not an option if someone has several foci, or if the focus is in an area essential for language. In certain cases when removing the focus was impossible, surgeons cut the corpus callosum to prevent epileptic seizures from crossing from one hemisphere to the other. One benefit was that, as predicted, the person's epileptic seizures affected only half the body. (The abnormal activity could not cross the corpus callosum.) A surprising bonus was that the seizures became less frequent. Evidently, epileptic activity rebounds back and forth between the hemispheres and prolongs a seizure. If it cannot bounce back and forth, a seizure may not develop at all. Although this surgery helped a fair number of patients, it has become obsolete, as other procedures have taken its place.

How does severing the corpus callosum affect other aspects of behavior? People with **split-brain syndrome**, those who have undergone surgery to the corpus callosum, maintain their intellect and motivation, they walk and talk normally, and they use their hands together on familiar tasks such as tying shoes. However, they struggle to use the hands together on tasks that they have not previously practiced (Franz et al., 2000).

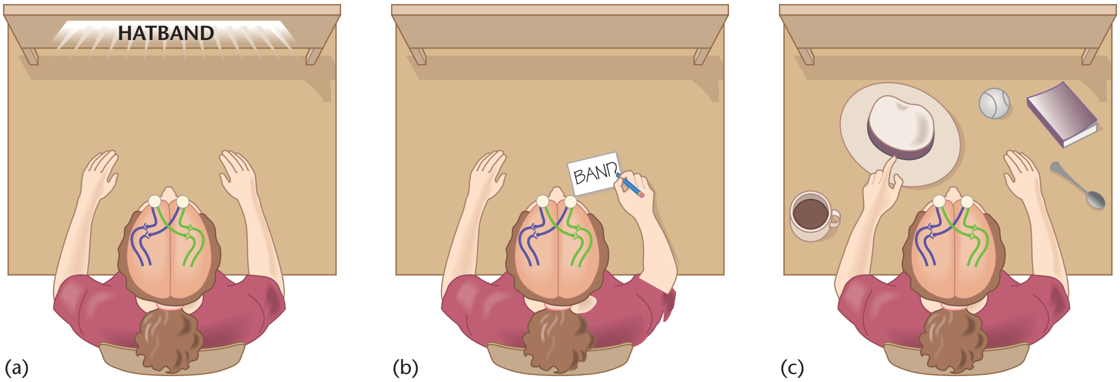
Try It Yourself

People with split-brain syndrome can use the two hands independently in ways that other people cannot. For example, try drawing ∪ with your left hand while simultaneously drawing ⊃ with your right hand. Most people find this task difficult, but those with split-brain do it with ease. Or try drawing circles with both hands simultaneously, but one of them just a little faster than the other. Most people find this task difficult, but split-brain people spontaneously draw circles at different speeds (Kennerley et al., 2002).

Research by Roger Sperry and his students revealed behavioral effects when stimuli were limited to one side of the body (Nebes, 1974). In a typical experiment, a person with split-brain syndrome stared straight ahead as the experimenter flashed words or pictures on one side of a screen, too briefly for the person to move the eyes (Figure 13.4). Information going to one hemisphere could not cross to the other, because of the damage to the corpus callosum. The person could point with the left hand to what the right hemisphere perceived, could point with the right hand to what the left hemisphere perceived, and could talk about anything the left hemisphere perceived. However, when the right hemisphere perceived something, the person would point to it with the left hand, while saying, "I don't know what it was. I didn't see anything." The talking left hemisphere did not know what the right hemisphere had seen.

Figure 13.4 Effects of damage to the corpus callosum

(a) When the word *hatband* is flashed on a screen, **(b)** a woman with split brain syndrome can report only what her left hemisphere perceived, "band." **(c)** However, with her left hand, she can point to a hat, which is what the right hemisphere perceived.



Occasional exceptions arise to this rule. Because a small amount of information travels between the hemispheres through several smaller commissures, as depicted in Figure 13.5, some persons with split-brain get enough information to give a partial description of what the right hemisphere saw (Berlucchi et al., 1997; Forster and Corballis, 2000).

Because the corpus callosum develops slowly, behaviors of young children occasionally resemble those of split-brain adults. In one study, 3- and 5-year-old children were asked to feel two fabrics, either with one hand at two times or with two hands at the same time, and say whether the materials felt the same or different. The 5-year-olds did equally well with one hand as with two. The 3-year-olds made 90 percent more errors with two hands than with one (Galin et al., 1979). The likely interpretation is that the corpus callosum matures sufficiently between ages 3 and 5 to facilitate the comparison of stimuli between the two hands.

Stop & Check

4. What can a person with split-brain do that other people cannot do?
5. Can a person with split-brain name an object after feeling it with their right hand? With their left hand? Explain.

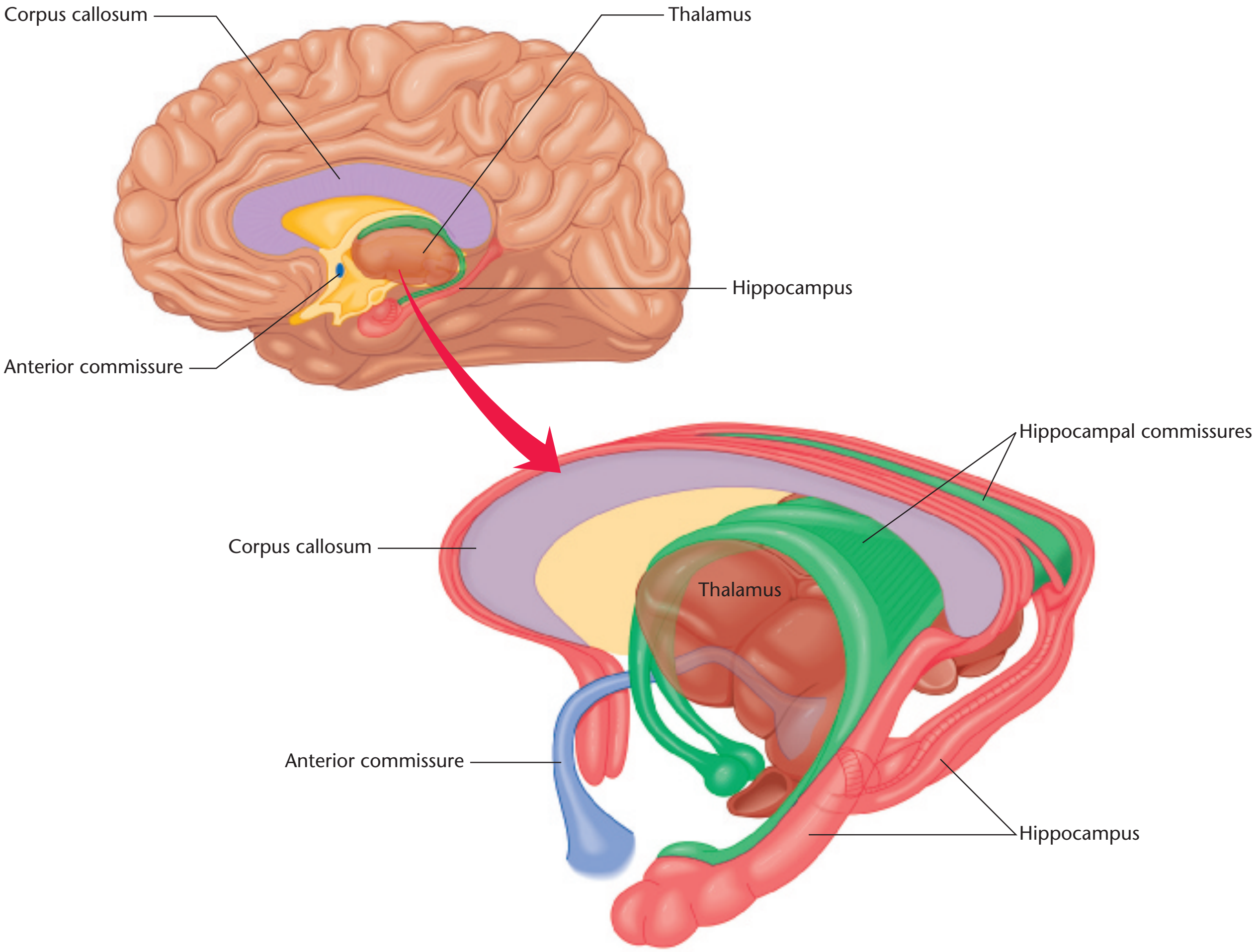
See page 439 for the answer.

Split Hemispheres: Competition and Cooperation

In the first weeks after split-brain surgery, the hemispheres act like separate people sharing one body. One person with split-brain repeatedly took items from the grocery shelf with one hand and returned them with the other (Reuter-Lorenz and Miller, 1998). She explained, "I'd reach with my right for the thing I wanted, but the left would come in and they'd kind of fight." She had similar problems when

Figure 13.5 The anterior and hippocampal commissures

These commissures exchange information between the two hemispheres, as does the larger corpus callosum.



(**Source:** Based on Nieuwenhuys, Voogd, & vanHuijzen, 1988, and others)

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she tried to get dressed, as each hand picked out different clothes and tried to put them on (Wolman, 2012). Another person's left hemisphere described the experience as follows:

> If I'm reading, I can hold the book in my right hand; it's a lot easier to sit on my left hand, than to hold it with both hands. . . . You tell your hand—I'm going to turn so many pages in a book—turn three pages—then somehow the left hand will pick up two pages and you're at page 5, or whatever. It's better to let it go, pick it up with the right hand, and then turn to the right page. With your right hand, you correct what the left has done. (Dimond, 1979, p. 211)

Such conflicts become less common over time. In some situations, the hemispheres learn to cooperate. A person with split-brain syndrome who was tested with the apparatus depicted in Figure 13.4 used an interesting strategy to answer a yes–no question about what he perceived in the left visual field. Suppose an experimenter flashes a picture in the left visual field and asks, "Was it green?" The left (speaking) hemisphere takes a guess: "Yes." That guess might be correct. If not, the right hemisphere, knowing the correct answer, makes the face frown. (Both hemispheres control facial muscles on both sides of the face.) The left hemisphere, feeling the frown, says, "Oh, I'm sorry, I meant 'no.'"

When the right hemisphere does something, the left hemisphere doesn't know why. How does it react? Rather than acting surprised, it invents an explanation. For example, if the right hemisphere perceives something pleasant or unpleasant, the left hemisphere feels the change of mood and might say, "What a beautiful wall that is!" or "Right now you are making me sad." In one study, experimenters flashed different pictures to the two hemispheres and asked the person to point to pictures associated with what was seen. In one case, a man's left hemisphere perceived a chicken claw and the right hemisphere saw a snow scene. The right hand then pointed to a picture of a chicken and the left hand pointed to a shovel. When asked to explain why he pointed at a shovel, he replied that you would need a shovel to clean out the chicken shed. From observations like these, Michael Gazzaniga (2000) proposed the concept of the **interpreter**, the tendency of the left hemisphere to invent and defend explanations for actions, even when the true causes are unconscious. This feature is not limited to persons with split-brain syndrome. We all think we know why we are doing something even when sometimes we don't.

The Right Hemisphere

After researchers discovered the importance of the left hemisphere for speech, they at first imagined the right hemisphere as something like a vice president, helping in a subordinate role but doing little unless the other hemisphere was damaged. Gradually observations revealed the right hemisphere's own important functions.

The right hemisphere is more adept than the left at comprehending spatial relationships. For example, one young woman with damage to her posterior right hemisphere had trouble finding her way around, even in familiar areas. To reach a destination, she needed directions with specific visual details, such as, "Walk to the corner where you see a building with a statue in front of it. Then turn left and go to the corner that has a flagpole and turn right. . ." (Clarke et al., 1993).

The right hemisphere is more responsive than the left is to the emotional tone of communication, which people express with gestures and tone of voice (Adolphs et al., 2002; Godfrey and Grimshaw, 2016). People with damage to the right hemisphere usually fail to understand humor and sarcasm (Beeman and Chiarello, 1998; Rosen et al., 2002). Happier mood tends to correlate with left-hemisphere activity, and depression is associated with increased activity in the right prefrontal cortex (Davidson, 1984; Jesulola et al., 2015). Increased right-hemisphere activity is also common in people who have recovered from depression, implying that it is a long-term predisposing factor rather than a reaction to depression (Vuga et al., 2006).

Here's something you can try: Ask someone to solve a verbal problem, such as, "See how many words you can think of that start with *sa-*," or "see how many words you can think of that end with -us." Unobtrusively watch the person's eye movements. Most people gaze to the right during verbal tasks, suggesting left hemisphere dominance, but most individuals with depression gaze to the left (Lenhart and Katkin, 1986).

Try It Yourself

In one fascinating study, people watched videotapes of 10 people. All 10 described themselves honestly during one speech and dishonestly during another. The task of the observers was to guess which of the two interviews was the honest one. The task is more difficult than you might guess, and most people are no more correct than chance. The group that performed best was people with left-hemisphere brain damage (Etcoff et al., 2000). They got only 60 percent correct—not great, but at least better than chance. People with an intact left hemisphere relied on the left hemisphere's analysis of what people were saying. Those with left-hemisphere damage relied on the right hemisphere's more intuitive reactions to emotional expressions. Could we all improve our liedetection by ignoring a speaker's words? Probably not. When people tried to guess whether German speakers were lying, people who spoke only English did no better than those who understood German (Law et al., 2018). If you have an intact left hemisphere, it insists on taking over in cases like this, even though it does a poor job.

In another study, 11 patients went through a procedure in which physicians anesthetized one hemisphere at a time by drug injection into one of the carotid arteries, which provide blood to the head. (This procedure, called the Wada procedure, is sometimes used before certain kinds of brain surgery.) When they were tested with the right hemisphere inactivated, something fascinating happened: They could still describe any of the sad, frightening, or irritating events they had experienced in life, but they remembered only the facts, not the emotion. One patient remembered a car wreck, another remembered visiting his mother while she was dying, and another remembered a time his wife threatened to kill him. But they denied they had felt any significant fear, sadness, or anger. When they described the same events with both hemispheres active, they remembered strong emotions. Evidently, when the right hemisphere is inactive, people do not experience strong emotions and do not even remember feeling them (Ross et al., 1994).

Stop & Check

6. Which hemisphere is dominant for the following in most people: speech, emotional inflection of speech, interpreting other people's emotional expressions, spatial relationships?
7. Some people offer to train you to use the right hemisphere of your brain more strongly, allegedly to increase creativity. If they were successful, can you see any disadvantage?

See page 439 for the answer.

Avoiding Overstatements

The research on left-brain/right-brain differences is exciting, but has sometimes led to unscientific assertions. Occasionally, you may hear a person say something like, "I don't do well in science because it is a left-brain subject, and I am a right-brain person." That kind of statement is based on two reasonable premises and one doubtful one. The scientific ideas are that (1) the hemispheres are specialized for different functions and (2) certain tasks evoke greater activity in one hemisphere or the other. The doubtful premise is that anyone habitually relies on one hemisphere more than the other.

What evidence do you suppose people have for believing, "I am a right-brain person"? Did they undergo an MRI or PET scan to determine which hemisphere was larger or more active? Not likely. Generally, when people say, "I am right-brained," their only evidence is that they perform well on creative tasks or poorly on logical tasks. Saying, "I am right-brained" sometimes implies that *because* I do poorly on logical tasks, *therefore,* I am creative. Unfortunately, illogical is not the same as creative.

Language Precursors in Other Species

During your childhood, you may have heard, watched, or read stories and cartoons about animals. In many of them, the animals talked, right? In real life, *why don't they?*

Nonhuman animals do communicate through visual, auditory, tactile, or chemical displays. Probably all vertebrates can learn the meanings of sounds. Many birds can imitate a sequence of sounds, and so can elephants, whales, and dolphins. At least some of the elements of language are widespread in the animal kingdom (Jarvis, 2019). The main thing that distinguishes human language from other species' communication is **productivity**, the ability for improvising unlimited combinations of signals to represent new ideas. A monkey might have one alarm call to indicate eagle in the air and another for snake on the ground, but it has no way to indicate eagle on the ground or snake in the tree (Cheney and Seyfarth, 2005).

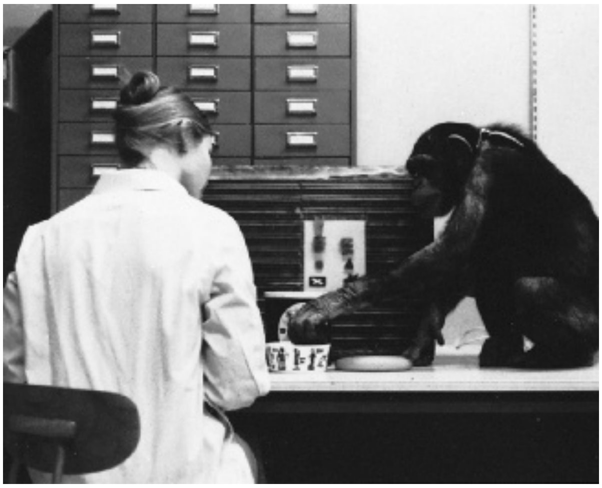
Chimpanzees

Several early attempts to teach chimpanzees to talk failed. However, chimpanzees in the wild do communicate with gestures, and investigators achieved better results by teaching them American Sign Language or other visual communication systems (Gardner and Gardner, 1975; Premack and Premack, 1972) (Figure 13.6). In one version, chimps learned to press keys bearing symbols to type messages on a computer, such as "Please machine give apple" or to another chimpanzee, "Please share your chocolate" (Rumbaugh, 1977).

The chimpanzees' use of symbols differed from human language in several ways. They seldom used symbols in new, original combinations, and they used symbols mainly to request, seldom to describe. However, they did demonstrate understanding. The chimp Washoe, trained in sign language, usually answered "Who" questions with names, "What" questions with objects, and "Where" questions with places, even when she used the wrong symbol for a name, object, or place (Van Cantfort et al., 1989).

Figure 13.6 An attempt to teach chimpanzees language

One of the Premacks' chimps, Elizabeth, reacts to colored plastic chips that read "Not Elizabeth banana insert—Elizabeth apple wash."



Courtesy of Ann Premack

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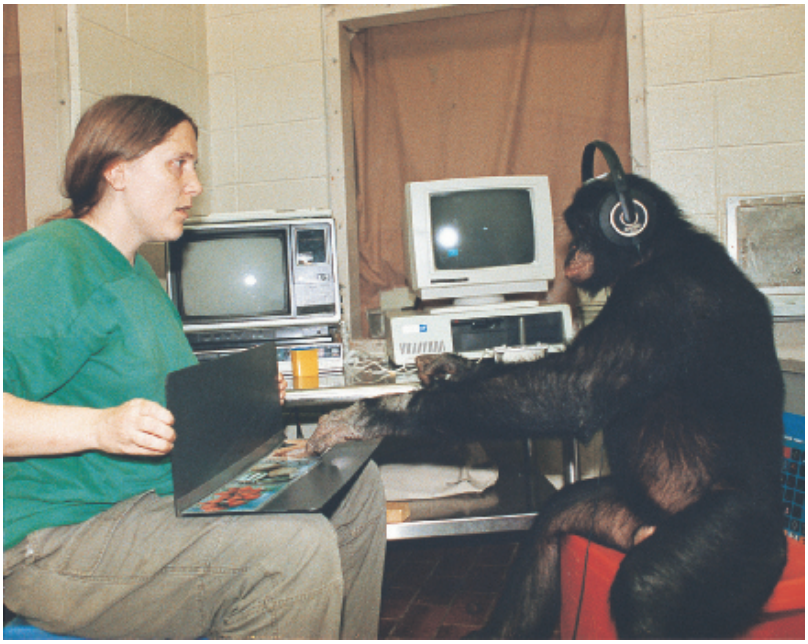
Bonobos

More promising results emerged from studies of a closely related species, *Pan paniscus,* known as the bonobo. Bonobos' social order resembles humans' in several regards. Males and females form strong attachments. They often copulate face to face. The female is sexually responsive on almost any day and not just during her fertile period. The males contribute significantly to infant care. Adults often share food. They stand comfortably on their hind legs. In short, they resemble humans more than other primates do.

Figure 13.7 Language tests for Kanzi, a bonobo *(Pan paniscus)*

Kanzi listens to questions through earphones and points to answers on a board. The experimenter does not hear the questions.



© Duane Rumbaugh/Georgia State University (Mr. Teodoro Ayllon)

(**Source:** From Georgia State University's Language Research Center, operated with the Yerkes Primate Center of Emory.)

In the mid-1980s, Sue Savage-Rumbaugh, Duane Rumbaugh, and their associates tried to teach a female bonobo named Matata to press symbols that represented words (Figure 13.7). Although Matata made little progress, her infant son Kanzi learned just by watching her. When given a chance to use the symbol board, he quickly excelled. Later, researchers noticed that Kanzi understood a fair amount of spoken language. For example, whenever anyone said the word *light,* Kanzi would flip the light switch. Kanzi and other bonobos developed language comprehension comparable to that of a typical 2- to 2½-year-old child (Hillix and Rumbaugh, 2003; Hillix et al., 2012; Savage-Rumbaugh, 1990; Savage-Rumbaugh et al., 1992; Savage-Rumbaugh et al., 1993):

- They understood more than they could produce.
- They followed unfamiliar, unlikely directions such as "Throw your ball in the river" or "Get the tomato in the microwave."
- They used symbols to name and describe objects even when they were not requesting them.
- They occasionally used symbols to describe past events. Kanzi once pressed the symbols "Matata bite" to explain the cut on his hand.
- They demonstrate creativity. A bonobo named Panbanisha asked, "Want milk sugar." Her trainer replied, "No, Panbanisha, I'd get in so much trouble. Here's some milk." Panbanisha replied, "Milk, sugar. Secret."

Why did bonobos develop more impressive skills than other chimpanzees? Perhaps they have more language potential than common chimpanzees. A second explanation is that these bonobos began language training when young. A third reason pertains to the method of training: Learning by observation and imitation (as humans do) promotes better language understanding than the formal training methods that previous studies used (Savage-Rumbaugh et al., 1992).

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Duane Rumbaugh, Sue Savage-Rumbaugh, and chimpanzee Austin

Chimpanzees and bonobos are outstanding teachers of psychology. They never presume that we, as their students, know a damn thing about who they are. And they certainly aren't impressed with our degrees. Consequently, they are able to teach all manner of important things about what it means to be human and to be ape—that is, if we as students are quiet, listen carefully, and let them tell us as only they can. (Duane Rumbaugh, personal communication)

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Stop & Check

8. What is the main difference between human language and the communication system of other species?

See page 439 for the answer.

Nonprimates

Certain aspects of language comprehension are not limited to primates. Dogs learn to understand words, sometimes a remarkable number. If you do a YouTube search for "Chaser the dog," you can find a border collie that learned more than a thousand English words. She also learned to understand simple grammar, such as the difference between the commands "to ball take Frisbee" and "to Frisbee take ball" (Pilley, 2013). As in humans, dogs' left hemisphere responds to words, whereas the right hemisphere responds to the emotional tone of voice (Andics et al., 2016).

Alex, an African gray parrot achieved some spectacular results (Figure 13.8). Parrots are, of course, famous for imitating sounds. Irene Pepperberg, a scientist well known for her work on animal cognition to improve emphasis/recognition of female scientists, demonstrated that parrots can use sounds meaningfully. She kept Alex in a stimulating environment and taught him by saying a word many times and offering rewards if Alex approximated the same sound. If he asked for an object, she gave him the object. In no case did she reward him with food for saying the name of something other than food.

Figure 13.8 Language tests for Alex

Alex conversed about objects in simple English—for example, answering, "What color is the circle?" He received no food rewards.

Rick Friedman/Corbis Historical/Getty Images

Gradually she moved on to more complex concepts (Pepperberg, 1981). In one test, Alex viewed a tray of 12 objects and correctly answered 39 of 48 questions such as "What color is the key?" (answer: "green") and "What object is gray?" (answer: "circle"). He also answered questions of the form "How many blue keys?" in which he had to count the blue keys among objects of two shapes and two colors (Pepperberg, 1994).

What do we learn from studies of nonhuman language abilities? At a practical level, we gain insights into how best to teach language to those who do not learn it easily. At a more theoretical level, these studies demonstrate that human language evolved from precursors present in other species. These studies also underscore the ambiguity of our concept of language. Language is not an all-or-nothing item.

How Did Language Evolve?

Reconstructing the evolution of language is necessarily speculative, because no examination of fossils will help. A popular hypothesis is that language evolved from communication by gestures (Corballis, 2012). We can communicate just by sound (a podcast or other recording), or just visually (reading), but normal face-to-face communication combines sounds with gestures, postures, and facial expressions. We ordinarily accompany speech with gestures, even if talking on a telephone, when the listener cannot see the gestures. Other primates communicate largely by gestures, supplemented with sounds. Children begin gesturing in the first year of life, and their use of gestures predicts how soon they will develop spoken language (Iverson and Goldin-Meadow, 2005).

Mouth gestures may be particularly important. Monkeys use several mouth gestures to communicate, including a lip-smacking gesture, which has a rhythm similar to speech. Monkeys are known to watch one another's mouth movements, especially when another is vocalizing, and it is plausible that the combination of sound plus mouth gesture could have been a precursor to spoken language (Ghazanfar, 2013).

With regard to the brain, what changed to make language possible? Most theories fall into two categories: (1) We evolved it as a by-product of overall brain development or (2) we evolved it as a specialization.

Is Language a By-Product of Intelligence?

One view is that language developed as an accidental by-product of increased intelligence that we evolved for other reasons. In its simplest form, this hypothesis faces several problems. It predicts that anyone with average intelligence should have normal language. In one family, 16 people over three generations have a dominant gene that impairs their language, despite otherwise normal intelligence (Fisher et al., 1998; Gopnik and Crago, 1991; Lai et al., 2001). They have trouble with even simple grammatical rules, as illustrated in the following dialogue about making plurals:

Experimenter	**Respondent**
This is a wug; these are . . .	How should I know? *[Later]* These are wug.
This is a zat; these are . . .	These are zacko.
This is a sas; these are . . .	These are sasss. *[Not sasses]*

In another test, experimenters presented sentences and asked whether each sentence was correct and, if not, how to improve it. Here is an example of an error:

Original Item	**Attempted Correction**
The boy eats three cookie.	The boys eat four cookie.

What about the reverse? Could a person with an intellectual impairment have good language? Psychologists would have answered "no," until they discovered **Williams syndrome**, a condition affecting about 1 person in 20,000, traceable to the loss of a gene that influences connections and myelin formation in the brain (Barak et al., 2019; Chailangkarn et al., 2016). Most people with this condition have intellectual impairment, although some are within the normal range (Miezah et al., 2020). Most have difficulty with attention, numbers, visuomotor skills (copying a drawing), and spatial perception (finding their way home). When asked to estimate the length of a bus, three people with Williams syndrome answered, "30 inches," "3 inches or 100 inches maybe," and "2 inches, 10 feet" (Bellugi et al., 2000).

AP Images/The Hutchinson News, Lindsey Bauman

People with Williams syndrome have a characteristic appearance, as well as a special set of behavioral strengths and weaknesses.

Many people with Williams syndrome develop surprisingly better language than one might expect based on their other intellectual performance. Here is a quote from a young woman with a moderate intellectual disability (Kozel et al., 2021):

> Lots of people don't know about Williams syndrome. Most doctors don't know about Williams syndrome. When I go to hospital, I always take an information sheet. I get bullied a lot. I think because of the way. . . oh this makes me feel sad. . . . I think because of the way I act some people don't realize it is hard to always be happy. I know this might sound stupid, but I can't tie my shoelaces. I wear shoes with elasticated shoelaces.

Let's not overstate the case. People with Williams syndrome may not handle language perfectly (Martens et al., 2008; Meyer-Lindenberg et al., 2006). Their grammar may be awkward, like that of someone who learned a second language late in life (Clahsen and Almazen, 1998; Karmiloff-Smith et al., 1998). They often use fancy words when a common word would work better, such as "I have to evacuate the glass" instead of "empty" or "pour out" the glass (Bellugi et al., 2000). Still, the possibility of developing better language abilities than other intellect implies that language is more than a by-product of overall intelligence.

Language as a Specialization

If language is not just a by-product of overall intelligence, it must have evolved as a specialized brain mechanism. Noam Chomsky (1980) and Steven Pinker (1994) proposed that humans have a **language acquisition device**, a built-in mechanism for acquiring language. Most children develop language so quickly and easily that it seems they must have been biologically prepared for this learning. Deaf children quickly learn sign language, and if no one teaches them a sign language, they invent one and teach it to one another (Goldin-Meadow et al., 1996; Goldin-Meadow and Mylander, 1998).

Researchers have explored the genetic basis of this preparation for language. The *FOXP2* gene regulates a protein that promotes synapse formation in the cerebral cortex and the basal ganglia (Chen et al., 2016; Lai et al., 2001). The human *FOXP2* gene differs from the chimpanzee version of that gene in just two bases, but those two mutations modified the human brain, jaw, and throat in ways that facilitate language development (Konopka et al., 2009). Remember that family whose members have such trouble with pronunciation and basic grammar? Their problem stems from a mutation in the *FOXP2* gene.

Another human specialization is that the part of our motor cortex that controls the vocal cords has greater connections to the rest of the cortex than in monkeys (Kumar et al., 2016). The greater connections enable more complex and detailed control of sound production. A change in the structure of the larynx also enables humans to increase the complexity of our sound production (Nishimura et al., 2022).

Why did humans evolve language and other species did not? One speculation is that language relates to the long period of dependency in childhood. Social interactions among people, including those between parents and children, favored the evolution of language. In that case, overall intelligence may be a by-product of language development more than language is a by-product of intelligence (Deacon, 1992, 1997).

Stop & Check

9. What evidence argues against the hypothesis that language evolution depended simply on the overall evolution of brain and intelligence?

See page 439 for the answer.

A Sensitive Period for Language Learning

If humans are specially adapted to learn language, perhaps we are adapted to learn best during a sensitive period early in life, just as sparrows learn their song best during their first few months. The consistent result is that adults have no trouble memorizing the vocabulary of a second language, but children have a great advantage on mastering grammar and pronunciation (Huang, 2014; Saito, 2013). A massive study of more than six hundred thousand people in many countries examined second language skills as a function of current age, age of starting a second language, and total years of practice. One conclusion was that it takes decades to master a second language, just as it does for the first. Those who started a second language at any age up to about 10–12 eventually achieved similar levels of proficiency. However, the ability to learn a foreign grammar apparently started declining after age 17 to 18, and people who started a second language after age 10–12 "ran out of time" to master the grammar before they reached that cutoff (Hartshorne et al., 2018). People who start learning a second language after age 10–12 almost never reach the level of a native speaker (Abrahamsson and Hyltenstam, 2009).

Another way to test the sensitive-period idea is to study people who learned no language during early childhood. Occasionally, hearing parents try teaching their deaf children only spoken language and lip-reading, until they eventually give up and introduce sign language. Children who begin sign language while still young learn much better than those who start later (Corina et al., 2020; Harley and Wang, 1997). A deaf child who learns sign language early can learn a spoken language later (although the pronunciation is generally poor), but a child who learns no language while young may have permanent impairment or difficulties at learning any kind of language (Mayberry et al., 2002). Those who do not begin learning sign language until after early adolescence do not even activate the usual language areas of the brain when they communicate (Mayberry et al., 2018). These observations clearly support the idea that childhood is a sensitive period for language development.

Stop & Check

10. What evidence supports a sensitive period for language learning?

See page 439 for the answer.

Brain Damage and Language

Another way to study specializations for language is to examine the role of various brain areas. Much of our knowledge has come from studies of people with brain damage.

Broca's Aphasia (Nonfluent Aphasia)

In 1861, the French surgeon Paul Broca treated the gangrene of a patient who had been mute for 30 years. When the man died 5 days later, Broca did an autopsy and found a lesion in the left frontal cortex. Over the next few years, Broca examined the brains of additional patients with **aphasia** (language impairment), and nearly always found damage that included this same area, which became known as **Broca's area** (Figures 13.9 and 13.10). Broca published his results in 1865, slightly later than reports by other French physicians, Marc and Gustave Dax, who also pointed to the left hemisphere as the seat of language abilities (Finger and Roe, 1996). Broca received the credit, however, because his description was more detailed and more convincing. This discovery, the first demonstration of the function of a particular brain area, paved the way for modern neurology.

When brain damage impairs language production, we call it **Broca's aphasia**, or **nonfluent aphasia**, regardless of the exact location of damage. Broca's area is not sharply defined anatomically, and damage produces only minor or brief language impairment unless it extends

Figure 13.9 Two areas important for language

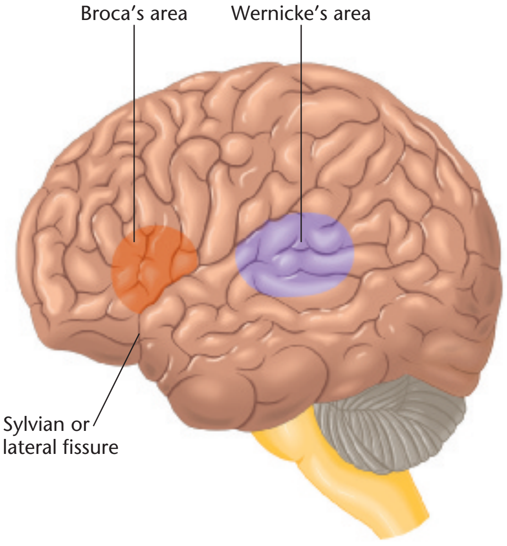

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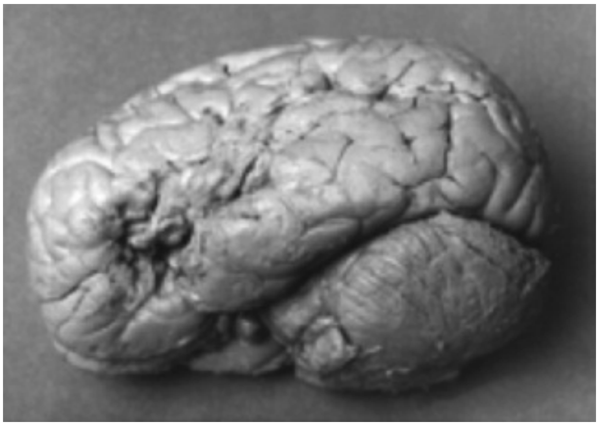
Figure 13.10 The brain of Broca's first patient

Damage in the left frontal cortex is apparent. MRI has revealed that the damage also extends deep into subcortical areas.



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(**Source:** Oxford Journals)

more broadly (Long et al., 2016). In fact, even in Broca's own cases, the damage was more extensive than he knew. Broca examined only the external surface of the brains, and then preserved some of them at the Musée Dupuytren in Paris, which still has them. Almost a century and a half later, researchers using magnetic resonance imaging demonstrated that the original cases of Broca's aphasia had damage extending deeper into the brain, including much of the basal ganglia (Dronkers et al., 2007). Today we recognize that Broca's aphasia relates to a broader area of damage. We also know that language relies on several parts of the cortex, including that of the right hemisphere, as well as parts of the thalamus, basal ganglia, and cerebellum (Hagoort, 2019).

Impaired Language Production

People with Broca's aphasia are impaired on all uses of language, including gestures and sign language (Cicone, et al., 1979; Trettenbrein et al., 2021). Broca's aphasia relates to language, not the vocal muscles. When you read a word aloud, looking at the word activates your visual system, which then exchanges information with Broca's area and surrounding areas, which then exchange information with your motor cortex. While you say something, your motor cortex controls the output, not Broca's area. Broca's area helps to organize speech, but it doesn't produce it (Flinker et al., 2015).

When people with Broca's aphasia speak, their speech is typically meaningful but sparse. For example, they might say, "Weather overcast" instead of "The weather is overcast." Although the results vary among individuals, they generally omit pronouns, prepositions, conjunctions, auxiliary (helping) verbs, quantifiers, and tense and number endings. At least that is the pattern for people speaking English. German- or Italian-speaking people with aphasia use more word endings, which are more essential than they are in English (Blackwell and Bates, 1995). Prepositions, conjunctions, helping verbs, and so forth are known as the *closed class* of grammatical forms because a language rarely adds new prepositions, conjunctions, and the like. In contrast, new nouns and verbs (the *open class*) enter a language frequently. People with Broca's aphasia seldom use the closed-class words. They may find it difficult to repeat a phrase such as "No ifs, ands, or buts." However, patients who cannot read aloud "To be or not to be" can read "Two bee oar knot two bee" (Gardner and Zurif, 1975). The trouble pertains to the word meanings, not pronunciation.

Problems in Comprehending Grammatical Words and Devices

People with Broca's aphasia understand most speech, except when the meaning depends on prepositions, word endings, or complex grammar—the same items that they omit when speaking. If they hear a sentence with complex grammar, such as "The girl that the boy is chasing is tall," they know that someone is tall and someone is chasing, but they don't know which is which (Zurif, 1980). Most English sentences are comprehensible without the prepositions and conjunctions. You can demonstrate this for yourself by taking a paragraph and deleting its prepositions, conjunctions, articles, helping verbs, pronouns, and word endings to see how it might appear to someone with Broca's aphasia. Here is an example, taken from earlier in this section. Note how understandable it is despite the deletions:

> ~~In~~ 1861, ~~the~~ French surgeon Paul Broca treat~~ed~~ ~~the~~ gangrene ~~of~~ ~~a~~ patient ~~who had~~ ~~been~~ mute ~~for~~ 30 year~~s~~. ~~When the~~ man die~~d~~ 5 day~~s~~ later, Broca ~~did an~~ autopsy ~~and~~ found ~~a~~ lesion ~~in the~~ left frontal cortex. ~~Over the~~ next few year~~s~~, Broca examine~~d~~ ~~the~~ brain~~s~~ ~~of~~ addition~~al~~ patient~~s~~ ~~with~~ aphasia (language impairment). ~~In~~ nearly all case~~s~~, ~~he~~ found damage (usual~~ly~~ stroke-relate~~d~~) ~~that~~ include~~d~~ ~~this~~ same area, ~~which is~~ now know~~n~~ ~~as~~ Broca~~'s~~ area.

People with Broca's aphasia have not totally lost their knowledge of grammar. They generally recognize that something is wrong with the sentence "He written has songs," even if they cannot say how to improve it (Wulfeck and Bates, 1991). In many ways, their comprehension problem is just an exaggeration of a tendency found in all of us. If you hear, "The ball kicked the girl," you might interpret it to mean the girl kicked the ball, thinking that you misheard the sentence, or maybe the speaker got confused and said it wrong (Ferreira et al., 2002). Suppose you hear someone say, "No head injury is too trivial to be ignored." Most people misinterpret this sentence (Paape et al., 2020). (Read it again, carefully.) Grammatically, it means that all head injuries should be ignored, even if they are trivial. Because that would be such a weird thing to say, we interpret

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it according to what seems more reasonable. Is the following a reasonable English sentence? "More people have been to Norway than I have." Many people impulsively say that it is, although they are baffled when asked to explain the meaning (Leivada, 2020). In short, all of us sometimes guess at the meaning and ignore the grammar, and even more so if we are not sure we heard it well. Patients with Broca's aphasia just rely on logical guesses more often.

Stop & Check

11. What kind of words are Broca's patients least likely to use?
12. What kind of words do Broca's patients have the most trouble understanding?

See page 439 for the answer.

Wernicke's Aphasia (Fluent Aphasia)

In 1874, Carl Wernicke (pronounced WER-nih-kee by most English speakers, although the German pronunciation is VAYR-nih-keh), a 26-year-old junior assistant in a German hospital, discovered that damage in part of the left temporal cortex produced a different kind of language impairment. Although patients could speak and write, their language comprehension was poor. Damage in and around **Wernicke's area** (Figure 13.10), located near the auditory cortex, produces **Wernicke's aphasia**, characterized by poor language comprehension and impaired ability to remember the names of objects. It is also known as **fluent aphasia**, because the person can still speak smoothly. As with Broca's aphasia, the symptoms and brain damage vary, and the damage generally extends into the thalamus and basal ganglia. We use the term *Wernicke's aphasia,* or *fluent aphasia,* to describe a certain pattern of behavior, regardless of the location of damage.

The typical characteristics of Wernicke's aphasia are as follows:

1. **Articulate speech.** In contrast to people with Broca's aphasia, those with Wernicke's aphasia speak fluently, except when pausing to try to think of the name of something. They have no trouble with prepositions, conjunctions, or grammar.
2. **Difficulty finding the right word.** People with Wernicke's aphasia have **anomia** (ay-NOME-ee-uh), difficulty recalling the names of objects. They make up names (e.g., "thingamajig"), substitute one name for another, and use roundabout expressions such as "the thing that we used to do with the thing that was like the other one." When they do manage to find some of the right words, they might arrange them improperly, such as, "The Astros listened to the radio tonight" (instead of "I listened to the Astros on the radio tonight") (R. C. Martin and Blossom-Stach, 1986).
3. **Poor language comprehension.** People with Wernicke's aphasia have trouble understanding speech, writing, and sign language. Impaired comprehension relates closely to difficulty remembering the names of objects.

Although Wernicke's area and surrounding areas are important, language comprehension also depends on the connections to other brain areas. For example, reading the word *lick* activates not only Wernicke's area but also the part of the motor cortex responsible for tongue movements. Reading *throw* activates the part of the premotor cortex controlling hand movements (Willems et al., 2010). Apparently when you think about an action word, you imagine doing it. Table 13.1 contrasts Broca's aphasia and Wernicke's aphasia.

Stop & Check

13. Describe the speech production of people with Wernicke's aphasia.
14. Describe the speech comprehension of people with Wernicke's aphasia.

See page 439 for the answer.

Bilinguialism

Many people guess that a bilingual person might rely on the left hemisphere for one language and the right hemisphere for the other. That is, at most, only partly true. Language production is predominantly controlled by the left-hemisphere in most people, regardless of how many languages they speak. At first, comprehension of a second language also depends on the left hemisphere, just as much as it does for a monolingual person. However, for people who become fluent in two or more languages, especially for people who are bilingual since infancy, hemispheric control of

Table 13.1 | Broca's Aphasia and Wernicke's Aphasia

Type	Pronunciation	Content of Speech	Comprehension
Broca's aphasia	Poor	Mostly nouns and verbs; omits prepositions and other grammatical connectives	Okay unless the meaning depends on complex grammar
Wernicke's aphasia	Unimpaired	Grammatical but often nonsensical; has trouble finding the right word, especially names of objects	Seriously impaired

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second language comprehension is variable (DeLuca et al., 2019; Gurunandam et al., 2020). It might depend mainly on the left hemisphere, the right hemisphere, or both hemispheres about equally.

As with almost anything else that people do, individual differences are prominent in the ability to learn languages. Some people master ten or more languages with apparent ease (Jouravlev et al., 2021). The biological basis for this variation is not known.

Dyslexia

Dyslexia is an impairment of reading by someone with adequate vision, motivation, cognitive skills, and educational opportunity. It is more common in boys than girls, and it exhibits high heritability, although no common genetic variant has a large effect. Dyslexia is especially common in English, which has so many words with irregular spellings. (Consider *ought, phlegm, bivouac, khaki, yacht, choir, physique,* and *gnat.*) However, dyslexia occurs in all languages, and it always pertains to a difficulty converting symbols into sounds (Ziegler and Goswami, 2005).

Many studies have reported abnormalities in the left hemisphere for people with dyslexia, even early in life, before children would be taught to read (Kraft et al., 2015; Kuhl et al., 2020; Raschle et al., 2012; van Zuijen et al., 2013; Xia et al., 2016). You might wonder how anyone knew to test certain children before they were old enough to display symptoms of dyslexia. The researchers identified families that include several people with dyslexia, and then tested young children, expecting (correctly) that many of them would develop dyslexia later.

A special area of the temporal cortex, adjacent to the area most responsible for facial recognition, is known as the **visual word form area**. Whereas facial recognition depends mainly on the right hemisphere, the visual word form area is more active in the left hemisphere. As people learn to read, this area becomes highly responsive to written words (Stevens et al., 2017). In blind people reading Braille, it responds to words in Braille (Kim et al., 2017). Damage to this area impairs reading without much effect on anything else (Canário et al., 2020). For children with dyslexia, researchers have reported that the visual word form area responds less strongly than average to words, and more strongly than average to other objects (Debska et al., 2021). That is, it is less selective.

Obviously, we did not evolve the visual word form area to help us read. Reading is far too recent in evolutionary terms (Arcaro and Livingstone, 2021). The area must have evolved to detect detailed shapes, and people invented written language in a way that takes advantage of this ability.

The limitation on conclusions about the brain mechanisms of dyslexia is that most studies have been small-scale, comparing ten to twenty people with dyslexia with a similar number of typical readers. Although the reported results usually fit with theoretical expectations, the risk of accidental or misleading findings is serious (Ramus et al., 2018).

One point that stands out about dyslexia is that different people have different kinds of reading problems, and no one explanation works for all. People can have auditory problems, impaired control of eye movements, or both (Judge et al., 2006). Some people have trouble sounding out words, so they try to memorize each word as a whole, and other people sound out words well enough, but they have trouble remembering all the irregularly spelled words (Flynn and Boder, 1991).

Hearing problems are common among people with dyslexia, but not the kind of problem that could be corrected with hearing aids. In fact, even some good musicians have dyslexia. The problem is impaired auditory memory, such as low accuracy at noting whether two sequences of tones, separated in time, were the same or different (Weiss et al., 2014). Many people with dyslexia have trouble detecting the temporal order of sounds, such as noticing the difference between beep-click-buzz and beep-buzz-click (Farmer and Klein, 1995; Kujala et al., 2000; Nagarajan et al., 1999). These results suggest a problem with how the brain handles auditory information, not a problem with the auditory information itself.

Many people with dyslexia also have alterations of attention (Facoetti et al., 2010). Here is a demonstration. Fixate your eyes on the central dot in each display below and, without moving your eyes left or right, try to read the middle letter of each three-letter display:

Try It Yourself

```
                NOE  •
                     • TWC
             WSH     •
                     •  EYO
          CTN        •
                     •     ONT
       HCW           •
                     •        OHW
    IEY              •
                     •           WCI
 HNO                 •
                     •              SIY
```

Most people find it easier to read the letters close to the fixation point, but many people with dyslexia are unusually adept at identifying letters well to the right of the fixation point. When they focus on a word, they are worse than average at reading it but better than average at

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perceiving letters 5 to 10 degrees to the right of it (Geiger et al., 1992; Lorusso et al., 2004). That kind of attentional focus would certainly confuse attempts at reading (De Luca et al., 1999). In many cases, people with dyslexia also have difficulties when letters are too crowded together (Gori and Facoetti, 2015). In short, dyslexia can result from a variety of problems.

Stop & Check

15. How does the visual word form area reportedly differ between dyslexic children and other children?
16. How is the visual word form area similar to the area responsible for facial recognition?

See page 439 for the answer.

Module 13.1 | In Closing

Language and the Brain

Many of the earliest home computers had no speech capacity, but users could plug in a device that would add speech, converting text output into sound. The evolution of human language was not like that. Our remote ancestors didn't just take a chimpanzee-type brain and add an independent module. Language required modifications throughout the brain. Trying to understand language is an important part of trying to understand what it means to be human.

Summary

1. The left hemisphere controls speech in most people, and each hemisphere controls mostly the hand on the opposite side, sees the opposite side of the world, and feels the opposite side of the body. **424**
2. In humans, the left visual field projects onto the right half of each retina, which sends axons to the right hemisphere. The right visual field projects onto the left half of each retina, which sends axons to the left hemisphere. **425**
3. After damage to the corpus callosum, each hemisphere can point or gesture to answer questions about the information that reaches it directly. However, because the left hemisphere controls speech in most people, only the left hemisphere of a split-brain person can give vocal answers about what it knows. **427**
4. Although the two hemispheres of a split-brain person are sometimes in conflict soon after the damage, they find ways to cooperate and cue each other. **428**
5. The right hemisphere is dominant for understanding and producing the emotional inflections of speech and for interpreting other people's emotional expressions. **429**
6. Several species have made significant progress in understanding language, especially bonobos. **430**
7. Language may have evolved from gestural communication. **432**
8. Two types of evidence argue against the idea that language emerged as a by-product of overall intelligence: Some people have normal intelligence but impaired language, and some people with Williams syndrome have better than expected language, considering their other cognitive impairments. **432**
9. People apparently have a sensitive period for language learning early in life. The ability to master a foreign grammar declines steadily after about age 17 to 18. Deaf children who do not get an opportunity to learn sign language when they are young are permanently disadvantaged at learning any type of language. **434**
10. People with Broca's aphasia (nonfluent aphasia) have difficulty speaking and writing. They find prepositions, conjunctions, and other grammatical connectives especially difficult. They also fail to understand speech when its meaning depends on complex grammar. **434**
11. People with Wernicke's aphasia (fluent aphasia) have trouble understanding speech and recalling the names of objects. **436**
12. Bilingual people rely on the left hemisphere for speech as much as other people do, but the hemispheric control of comprehension is variable. **436**
13. Dyslexia (reading impairment) has many forms, resulting from diverse causes. **437**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

anomia	**436**
aphasia	**434**
Broca's aphasia (nonfluent aphasia)	**434**
Broca's area	**434**

corpus callosum **424**
dyslexia **437**
fluent aphasia **436**
interpreter **429**
language acquisition device **433**
lateralization **424**
nonfluent aphasia **434**
optic chiasm **425**
planum temporale **425**
productivity **430**
split-brain syndrome **427**
visual field **425**
visual word form area **437**
Wernicke's aphasia (fluent aphasia) **436**
Wernicke's area **436**
Williams syndrome **433**

Thought Questions

1. Presumably evolution equipped the left and right hemispheres with different functions for a reason. What might it be?
2. Most people with Broca's aphasia suffer from partial paralysis on the right side of the body. Most people with Wernicke's aphasia do not. Why?
3. In a syndrome called *word blindness,* a person loses the ability to read (even single letters), although the person can still see and speak. What is a possible neurological explanation? That is, can you imagine a pattern of brain damage that might produce this result?

Stop & Check Answers

1. In young people, both hemispheres have some speech abilities. By adulthood, most people have suppressed the right hemisphere's speech activity.
2. In guinea pigs, the right eye is far to the side of the head and sees only the right visual field. In humans, the eyes point straight ahead, and half of each eye sees the right visual field.
3. The left half of each retina receives input from the right half of the world and sends output to the left hemisphere, enabling the left hemisphere to see the right half of the world. This may be easier to remember if you draw a sketch of the connections, similar to Figure 13.3.
4. A split-brain person can draw different things with their two hands at the same time, or move the hands at different speeds at the same time.
5. A split-brain person can describe something after feeling it with their right hand but not with their left. The right hand sends its information to the left hemisphere, which is dominant for speech in most people. The left hand sends its information to the right hemisphere, which cannot speak.
6. The left hemisphere is dominant for speech. The right hemisphere is dominant for the other items listed.
7. People with predominant right-hemisphere activity exhibit an increased tendency toward depression.
8. Human language has productivity, the ability for improvising combinations of symbols to express new ideas.
9. Some people have average intelligence but poor language, and some people with intellectual disabilities develop better than expected language.
10. People who start learning a second language after about age 10–12 almost never master the grammar like a native speaker. Deaf children who did not learn a language, including sign language, while young do not become proficient at it.
11. They have the greatest trouble with "closed-class" words that are meaningful only in the context of a sentence, such as prepositions, conjunctions, and helping verbs.
12. They have the most trouble understanding the same kind of words they have trouble producing—the closed-class words.
13. People with Wernicke's aphasia speak fluently and grammatically but omit most nouns and therefore make little sense.
14. People with Wernicke's aphasia have trouble understanding speech.
15. For children with dyslexia, this area is less selective, responding to other objects as well as words.
16. They are side by side in the temporal cortex, and both respond to detailed patterns that people learn to recognize.

Module 13.1 | End-of-Module Quiz

1. As children grow older and improve their language, what happens to the right hemisphere's ability to control speech?
   - **a.** It gradually increases.
   - **b.** It remains at zero.
   - **c.** The left hemisphere suppresses it.
   - **d.** It decreases, except in bilingual people.

2. At the human optic chiasm, which axons cross to the opposite hemisphere?
   - **a.** Those from the nasal (inside) half of each retina
   - **b.** Those from the temporal (outside) half of each retina
   - **c.** Those from the center of each retina
   - **d.** All the axons from each retina

3. What does the right hemisphere see?
   - **a.** The left visual field, by means of the left eye
   - **b.** The right visual field, by means of the left eye
   - **c.** The left visual field, by means of the right half of each retina
   - **d.** The right visual field, by means of the left half of each retina

4. When can a person with split-brain syndrome say what a hand feels?

a. After feeling it with either hand
b. Only after feeling it with both hands at the same time
c. Only after feeling it with the left hand
d. Only after feeling it with the right hand

5. What did Gazzaniga mean by "the interpreter"?

a. Similarities between monkey gestures and human speech
b. The ability to perceive similarities between written and spoken language
c. The exchange of information between the left and right hemispheres
d. People's attempts to make up explanations for their behaviors

6. Which aspect of language does the right hemisphere control better than the left?

a. Production and understanding of prepositions and conjunctions
b. Understanding complex grammar
c. Understanding emotional expressions
d. Memorizing long passages

7. What is a likely explanation for bonobos' success at understanding speech?

a. Bonobos' brains have larger neurons than most other primates.
b. The experimenters combined both classical and operant conditioning.
c. The bonobos spent much time with human children.
d. The bonobos started young and learned by imitation.

8. What is the theoretical importance of Williams syndrome?

a. It demonstrates that language evolved from the use of gestures.
b. It demonstrates that the two hemispheres control different aspects of behavior.
c. It demonstrates the possibility of good reading despite poor vision
d. It demonstrates that language is more than a byproduct of intelligence.

9. The *FOXP2* gene differs between which two groups?

a. Males and females
b. Humans and chimpanzees
c. Dyslexics and neurotypical readers
d. Bilinguals and monolinguals

10. The ability to master a foreign grammar begins to decline steadily after what age?

a. 6 months
b. 2 years
c. 17–18 years
d. 60–70 years

11. People with Broca's aphasia are most impaired on producing and understanding which type of words?

a. Common nouns
b. Proper nouns
c. Prepositions and conjunctions
d. Verbs

12. Which of the following is characteristic of Wernicke's aphasia?

a. Difficulty forming new long-term memories, especially episodic memories
b. Inability to describe anything seen in the left visual field or felt with the left hand
c. Poor pronunciation and difficulty using and understanding grammar
d. Difficulty remembering names of objects

13. The visual word form area is near, but in the opposite hemisphere, from the area responsible for control of what?

a. Grammatical understanding
b. Facial recognition
c. Working memory
d. "The interpreter"

Answers: 1c, 2a, 3c, 4d, 5d, 6c, 7d, 8d, 9b, 10c, 11c, 12d, 13b.

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Module 13.2

Consciousness

Learning Objectives

After studying this module, you should be able to:

10. Explain why nearly all neuroscientists and philosophers favor some version of monism with regard to the mind–brain relationship, and discuss the identity position.

11. Describe the brain activities that differ between conscious and unconscious processing of a stimulus, and the research supporting these conclusions.

12. Discuss and evaluate proposed methods of determining whether an unresponsive person might be conscious.

13. Describe the brain mechanisms of attention.

> [W]e know the meaning [of consciousness] so long as no one asks us to define it.
>
> William James (1892/1961, p. 19)

What is consciousness, and how does it relate to brain activity? We shall consider those questions first from a philosophical standpoint and then from a research standpoint.

The Mind–Brain Relationship

Suppose you say, "I was frightened because I thought someone was chasing me." A neuroscientist says, "You were frightened because of increased electrochemical activity in the following areas of your brain. . . ." If both statements are true, what is the relation between them?

Biological explanations of behavior raise the **mind–body** or **mind–brain problem**: How does mental experience relate to brain activity? The philosopher René Descartes defended **dualism**, the belief in separate mind and body, but he recognized the issue of how a non-material mind could influence a physical brain. He proposed that mind and brain interact at a single point in space, which he suggested was the pineal gland, the smallest unpaired structure he could find in the brain (Figure 13.11).

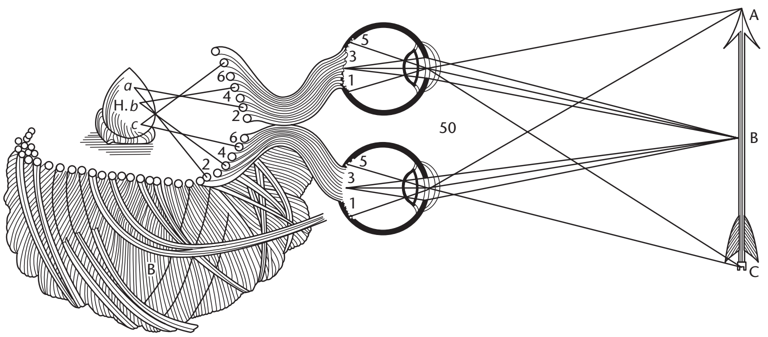
Although we credit Descartes with the first explicit defense of dualism, he hardly originated the idea. Our experiences seem so different from brain activity that most people take it for granted that mind and brain must be different. Even outstanding psychologists sometimes lapse into dualistic thinking. One psychologist commented, "we know little about . . . whether neural events drive psychological events, or the converse" (G. A. Miller, 2010, p. 716). In other words, we don't know whether brain activity causes thoughts or whether thoughts cause brain activity. But if thoughts and brain activity are the same thing, the question doesn't make sense.

Nearly all current philosophers and neuroscientists reject dualism. A decisive objection is that dualism conflicts with one of the cornerstones of physics, known as the law of the conservation of matter and energy: Matter and energy cannot be created or destroyed, and neither one changes except by the influence of other matter or energy. Unless our understanding of physics is totally wrong, a mind that is not made of matter or energy could not do anything, not even move a muscle. If you use a term like *mind* to mean a ghostlike something that is neither matter nor energy, don't underestimate the scientific and philosophical arguments that can be marshaled against you (Dennett, 1991).

The alternative to dualism is **monism**, the belief that the universe consists of only one kind of substance. Nearly all neuroscientists accept some version of monism. As far as we can tell, you cannot have mental activity without

Figure 13.11 René Descartes's conception of brain and mind

Descartes understood how light from an object (the arrow) reached the retinas at the back of the eyes. The letters and numbers represent pathways that he imagined from the retinas to the pineal gland. (His guesses about those pathways were wrong.)



(**Source:** From Descartes's *Treatise on Man*)

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brain activity, and you cannot have certain types of brain activity without mental activity. Various forms of monism are possible, characterized as materialism, mentalism, and identity.

Materialism is the view that everything that exists is physical. One version of materialism holds that we will eventually see how to explain consciousness in purely mechanical terms, even though we don't see how to do so now. Biologists have explained digestion, reproduction, blood circulation, and other processes in physical and chemical terms, and so we might expect that consciousness will yield to a similar explanation. However, this idea is not self-evident. Consciousness might be different from other body functions.

According to another version of materialism, "eliminative materialism," mental events don't even exist (Churchland, 1986; Graziano, 2013; Norretranders, 1998). Most of us find it hard to believe that the mind is a figment of our imagination. Rene Descartes said that the only thing he could not doubt was "I think, therefore I am." Several other psychologists have argued that consciousness exists, but we can ignore it, because it does not help us explain behavior (Lashley, 1923; Wegner, 2002). However, consciousness is not something that psychologists invented to try to explain behavior. It is the observation itself, something we are trying to explain.

Mentalism is the view that nothing could exist unless a mind is aware of it. The philosopher George Berkeley was the original defender of this position, and Donald Hoffman (2019) later stated it in revised form: To exist is to be perceived, and anything that is not perceived does not exist. This has never been a popular view among scientists, but it is not easy to test. (You are welcome to try.)

The **identity position** is the view that conscious experiences and certain brain activities are the same thing. By analogy, you could describe the *Mona Lisa* as a beautiful painting, or you could list the color and brightness of each point on the painting. Although the descriptions appear different, they refer to the same item. According to the identity position, brain activity does not cause conscious experiences, and conscious experiences do not cause brain activity. The brain activity *is* the conscious experience. This view has metaphysical implications. The profoundest questions that people ask are why the universe exists and why, in a universe of matter and energy, consciousness exists. Just between you and me, and don't tell anyone I said so, but I think the identity position implies that the two questions are linked: Maybe we can't understand consciousness without understanding the universe, and maybe we can't understand the universe without understanding consciousness.

David Chalmers (1995) distinguished between what he calls the easy problems and the hard problem of consciousness. The easy problems pertain to such questions as what brain activity occurs during consciousness that does not occur during unconsciousness. Questions like that are difficult scientifically but not philosophically. The **hard problem** concerns why consciousness exists at all. As Chalmers (1995, p. 203) put it, "Why doesn't all this information-processing go on 'in the dark,' free of any inner feel?" The question was noted by Baruch Spinoza, and before him by Aristotle, who wrote in *De Anima*, "They attach the soul to, and enclose it in, body without further determining why this happens… And yet some such explanation would seem to be required." Still today, some explanation is required.

The philosopher Chalmers (2007), the biologist Bernhard Rensch (1977), and the physicist Roger Penrose (2001) suggested that consciousness may be a fundamental property of matter. A fundamental property is one that cannot be explained in terms of something else. Electrical charge is one example. Maybe consciousness is like that. However, to call consciousness a fundamental property would mean only that we have given up on explaining it, and it is certainly too soon for that.

Why does consciousness exist? One possibility is consciousness evolved as an "add-on" feature of brain functioning that evolved to improve our ability to survive and reproduce. But what behaviors would be unexplainable without consciousness? Okay, one example is the behavior of talking about consciousness. Presumably we would not talk about it if we did not experience it. Another example is the behavior of staring in awe at a scene of natural beauty. It would be awkward to explain that behavior without some appeal to the conscious experience. But surely we did not evolve consciousness just for the purpose of talking about it, or for staring at sunsets. Roy Baumeister (Baumeister et al., 2011) noted that consciousness always accompanies decision making. Indeed it does, but "accompanying human decision making" is not the same as "necessary for decision making." Self-driven cars make decisions. Stanislas Dehaene (2014) notes that consciousness is necessary when we perform complex tasks, such as mentally multiplying 12 × 13. Yes, humans are always conscious when they do that, but computers perform the same tasks, presumably without consciousness. Engineers continue programming artificial intelligence to perform ever more complicated tasks, without equipping the machines with consciousness. (At least we assume they are unconscious.) If artificial intelligence does not need consciousness, then it is not obvious why evolution needed to add consciousness to brain functioning.

If consciousness is not an add-on feature that enables complex behavior, the alternative is that it emerges necessarily from the properties of brain activity. By analogy, the emergent properties of water emerge necessarily from the properties of hydrogen and oxygen atoms when they combine chemically. To say that consciousness emerges necessarily from brain activity means that the universe is set up in such a way that certain types of neuronal activity automatically become conscious.

According to the identity position, consciousness does not explain any behavior that brain activity does not explain, because consciousness is the same thing as brain activity. When you think something, it is because the laws of physics bounced certain electrons in certain ways, but it is equally true that the electrons bounced in those ways because of the logic behind your thinking.

Stop & Check

17. Why do nearly all scientists and philosophers reject the idea of dualism?
18. What is meant by the “hard problem”?

See pages 450-451 for the answer.

Consciousness of a Stimulus

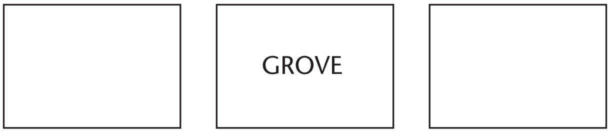
Most scientists (e.g., Crick and Koch, 2004) agree that we cannot answer the hard problem, at least at present. As one article insightfully pointed out, brain mapping tells us why lemon smells similar to orange, but not why lemon smells like lemon (Pashkovski et al., 2020). The best we can do is answer questions like what brain activity is necessary for consciousness. Starting with the answerable questions is always the best strategy.

Consciousness of a stimulus is a private experience. A simple machine could be programmed to say “blue” when it receives light from a cloudless sky, but when you view the same sky, you have an internal experience. Because that internal experience is unobservable, researchers rely on this operational definition: Someone who reports awareness of one stimulus and not another was **conscious** of the first and not the second. This definition does not imply that preverbal children, animals, or brain-damaged people are unconscious. It just means that we seldom use them in research on consciousness, and if we do, we need to find a way for them to indicate awareness or unawareness of a stimulus.

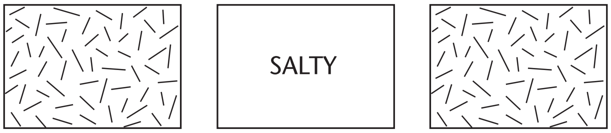
Through most of the twentieth century, psychological researchers avoided the topic of consciousness altogether. Modern methods have made consciousness research respectable because researchers can record brain activity while using procedures that permit or prevent conscious perception of a stimulus. One procedure is called **flash suppression** (Kreiman et al., 2002). Suppose you see a yellow dot. Then, while the dot remains on the screen, other dots around it flash on and off. While they are flashing, you do not see the stationary dot. The strong response to the flashing dots decreases awareness of the steady dot, as well as the brain’s response to it (Yuval-Greenberg and Heeger, 2013). Similarly, suppose you see a yellow dot, and then blue dots all around it start moving rapidly. The moving blue dots grab your attention so strongly that the yellow dot seems to disappear for a few seconds, reappear for a few seconds, disappear again, and so forth (Bonneh et al., 2001).

Experiments Using Masking

Many studies use **masking**: A brief visual stimulus is preceded, followed, or both by longer interfering stimuli. Stanislas Dehaene and colleagues (Dehaene et al., 2001) flashed a word on a screen for just 29 milliseconds (ms). On some trials, it was preceded and followed by a blank screen:



In these cases, people identified the word almost 90 percent of the time. On other trials, the researchers flashed a word for the same 29 ms but preceded and followed it with masking patterns:



In the masking condition, people usually said they saw no word at all. Using fMRI and evoked potentials, the researchers found that the stimulus initially activated the primary visual cortex in both the conscious and unconscious conditions. In the conscious condition (no masking), the activity spread to additional brain areas, including the prefrontal cortex and parietal cortex, which amplified the signal and reflected it back to the visual cortex, magnifying and prolonging its effect there. For people with damage to the prefrontal cortex, a visual stimulus has to last longer than average in order to become conscious (Del Cul et al., 2009). In the unconscious condition (masking), the stimulus spread only weakly to areas beyond the primary visual cortex, and nothing reflected it back to magnify the initial response.

Courtesy of Stanislas Dehaene

Stanislas Dehaene

Throughout the nineteenth and twentieth centuries, the question of consciousness lay outside the boundaries of normal science. . . . For many years, no serious researcher would touch the problem. . . . When I was a student in the late 1980s, I was surprised to discover that during lab meetings, we were not allowed to use the C-word. . . . And then in the late 1980s everything changed. Today the problem of consciousness is at the forefront of neuroscience research. (Dehaene, 2014, pp. 7–8)

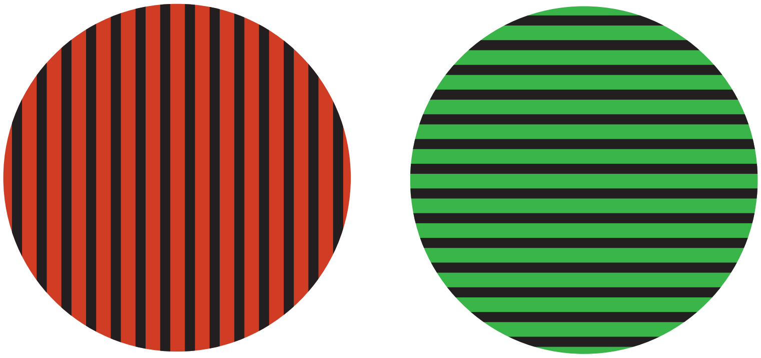
A similar study found that the difference in brain response, depending on whether a stimulus is destined to be conscious or not, emerges 200 milliseconds (ms) after onset of the stimulus, reaches maximum at 500 ms, and continues for the next 2 to 3 seconds. That study also found that consciousness of one stimulus inhibited responses to other simultaneous stimuli (Q. Li et al., 2014). That is, stimuli compete for your attention.

A conscious stimulus also synchronizes neurons' responses (Eckhorn et al., 1988; Gray et al., 1989; Melloni et al., 2007; Womelsdorf et al., 2007). When you see something and recognize it, it evokes precisely synchronized activity in several brain areas, in the frequency of about 30 to 50 Hz (cycles per second), known as *gamma waves* (Doesburg et al., 2009; Fisch et al., 2009). One consequence of synchronized action potentials is that their synaptic inputs arrive simultaneously at their target cells, producing maximal summation (Fell and Axmacher, 2011).

Overall, the data imply that consciousness of a stimulus depends on the amount and spread of brain activity. Becoming conscious of something means that its information takes over more of your brain's activity, and rebounds to magnify the initial activity.

Figure 13.12 Binocular rivalry

If possible, look at the circles through tubes, such as those from inside rolls of toilet paper or paper towels. Arrange so that the left eye sees only the left image and the right eye sees only the right image. Otherwise, touch your nose to the center so that your eyes see different images. The two views will compete for your consciousness, and your perception will alternate between them. Occasionally, you might see part of one image and part of the other.



Stop & Check

19. How did Dehaene and colleagues control whether a stimulus would or would not be consciously perceived?
20. In this experiment, how did the brain's responses differ to the conscious and unconscious stimuli?

See page 451 for the answer.

Experiments Using Binocular Rivalry

Try It Yourself

Here is another way to make a stimulus unconscious. Look at Figure 13.12, but hold it so close to your eyes that your nose touches the page, right between the two circles. Better yet, look at the two parts through a pair of tubes, such as the tubes inside rolls of paper towels or toilet paper, or roll up your hands like tubes. In one way or another, arrange it so that you see red and black vertical stripes with your left eye, and green and black horizontal stripes with your right eye. Close one eye and then the other to make sure your eyes see completely different patterns. Then open both eyes and notice what happens. Seeing something requires perceiving *where* it is, and the red vertical stripes cannot be in the same place as the green horizontal stripes. Because your brain cannot perceive both patterns in the same location, your perception alternates between the two. The inferior (lower) frontal cortex responds to conflicting perceptions by temporarily inhibiting one or the other (Weilnhammer et al., 2021). For most people, each perception lasts about 2 to 5 seconds before the other replaces it, although some people switch faster or slower (Blake, 2022; van Loon et al., 2013). These shifts, demonstrating **binocular rivalry**, are gradual, sweeping from one side to another. You can voluntarily shift your attention to one or the other image, but only temporarily (Paffen and Alais, 2011). Instead of lines, the stimuli could be other images, such as a house versus a face.

The two images do not necessarily share your attention equally. Some people see with one eye longer than the other. Also, an emotionally charged image, such as a face with an emotional expression, holds attention longer than a neutral image (Yoon et al., 2009). A happy face holds attention longer for someone in a happy mood, and a scowling face holds attention longer for someone in a sad mood (Anderson et al., 2011; Anderson et al., 2013).

The competing stimuli evoke brain responses that researchers can measure. Both the red–black and green–black patterns you just experienced were stationary. To make the brain responses easier to distinguish, researchers presented to one eye a stationary stimulus and to the other eye a pattern that pulsated several times per second in size and brightness. Then they recorded brain activity in several areas. At times when people reported consciousness of the pulsating stimulus, activity at the same rhythm was prominent in much of the brain, as depicted in Figure 13.13. When people reported consciousness of the stationary stimulus, the pulsating brain activity was weak (Cosmelli et al., 2004). The conclusion is that a conscious stimulus strongly activates much of the brain. When the same stimulus is unconscious, it produces weaker and less widespread activity. A related study found that when someone switched between one perception and the other, the brain response changed first in the occipital cortex, and then spread to the other areas (de Jong et al., 2016).

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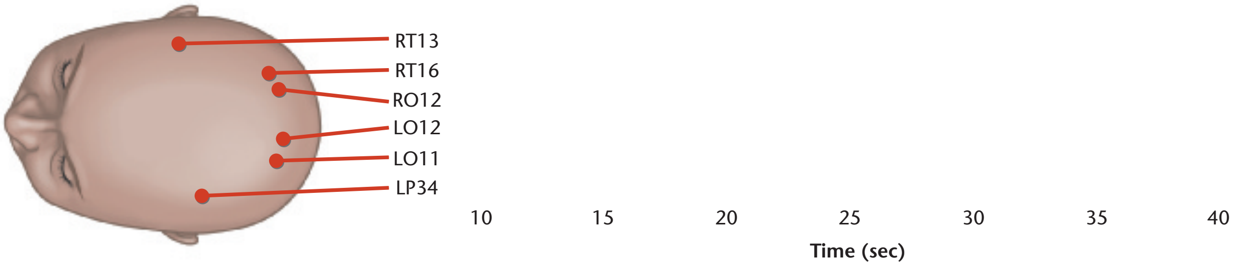
Figure 13.13 Brain activity during binocular rivalry

When the person reported seeing the pulsating stimulus, neurons throughout much of the brain responded vigorously at the same rhythm as the stimulus. When the person reported the stationary stimulus, the rhythmic activity subsided.



(**Source:** Reprinted from "Waves of consciousness: Ongoing cortical patterns during binocular rivalry," by D. Cosmelli et al., 2004, *NeuroImage*, *23*(1), 128–140)

One more curious point about binocular rivalry: If the images confronting the two eyes are almost the same, your brain fuses them into one. If they are clearly different, you get binocular rivalry. At an intermediate stage between almost the same and clearly different, you alternate between fusing the images and binocular rivalry (Riesen et al., 2019). Figure 13.14 is an example. Your brain does its best to make sense of the goofy stuff you are showing it.

The Fate of an Unattended Stimulus

During binocular rivalry, while you are attending to the stimulus in one eye, your brain does not completely discard information from the other eye. If a new stimulus suddenly flashed in that eye, it would immediately capture your attention. Suppose a word fades onto the screen gradually, and you are to report the time when your attention shifts to the previously unattended eye. If it is a word from your own language, it captures your attention faster than a word from a language you do not understand (Jiang et al., 2007). Other experiments with either binocular rivalry or flash suppression have demonstrated that you more rapidly become aware of faces and other social stimuli than nonsocial stimuli, and more rapidly become aware of a signal previously associated with danger than a safe stimulus (Gayet et al., 2016; Su et al., 2016). If you have a strong interest in something—cars, for example—a picture of that kind of object gains your awareness more readily than it does for other people (Stein et al., 2016). Given that you become aware of a highly meaningful item faster than something less meaningful, evidently your brain must have decided that the stimulus was meaningful *before* you became conscious of it! Much brain activity is unconscious, and unconscious activity can influence behavior.

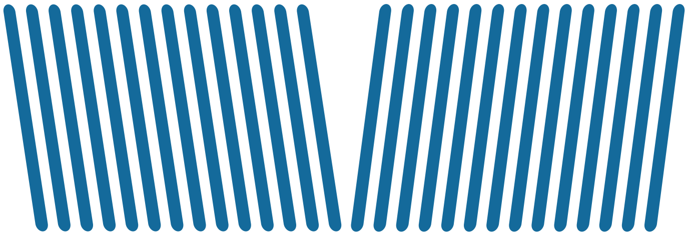
Stop & Check

21. How could someone use brain recordings to determine which of two patterns in binocular rivalry is conscious at a given moment?
22. If you are aware of one stimulus in a case of binocular rivalry, what evidence indicates that your brain is also processing the other one?

See page 451 for the answer.

Figure 13.14 Alternation between fused images and binocular rivalry

If possible, look at the circles through tubes, such as those from inside rolls of toilet paper or paper towels. Arrange so that the left eye sees only the left image and the right eye sees only the right image. Otherwise, touch your nose to the center so that your eyes see different images. You will sometimes experience binocular rivalry, and at other times fuse the two images into one. Based on the report by Riesen et al. (2019).



What Is Important about the Cerebral Cortex?

Consciousness is associated with vigorous activity in the cerebral cortex. People who have had surgical removal of the cerebellum experience no loss of consciousness, even though the cerebellum has far more neurons and synapses than the cortex. Evidently consciousness does not depend on the total number of neurons. Total amount of activity also fails to define consciousness. During an epileptic seizure, neuronal activity is high, but it lacks informative patterns, and consciousness ceases.

Marcello Massimini and Giulio Tononi (2018) explored the key differences between conscious and unconscious activity. Their conclusion was

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that consciousness requires the integration of information. If your brain had no task other than detecting the presence of light, or detecting sound waves, consciousness would be irrelevant. But you integrate information. You compare the light in one part of the retina to the light in another part. You detect that a light and a sound came from the same direction or different directions, or that the light predicts the sound, or any of other possible relationships among the stimuli that you can detect. The cerebral cortex, unlike the cerebellum, has long-range reciprocal connections enabling each area to influence many others and receive feedback from the others. Those connections enable information to spread, compare, and interact.

Stop & Check

23. How do cortical connections differ from cerebellar connections?

See page 451 for the answer.

The Timing of Consciousness

Are you conscious of events instant by instant as they happen? It certainly seems that way, but if there were a short delay between an event and your consciousness of it, how would you know? You wouldn't. Perhaps you construct a conscious experience after the event.

Consider the **phi phenomenon** that perceptual researchers noted long ago: In the simplest case, you see a dot alternating between one position and another, side by side. It appears to move between the two positions, even though you never see it in the space between them. It is an interesting illusion, but *when* did you see it move? When you saw it in the first position, you didn't know it was going to appear in the second position. Evidently, you perceived it as moving from one position to the second after it appeared in the second position! In other words, the second position changed your perception of what occurred before it.

Another example: Suppose you hear a recorded word that is carefully engineered to sound halfway between *dent* and *tent*. Let's call it **ent.* If you hear it in the phrase "*ent in the fender," it sounds like *dent.* If you hear it in the phrase "*ent in the forest," it sounds like *tent.* Later words changed what you heard before them (Connine et al., 1991).

One more example: Suppose you are watching a screen that at unpredictable times displays a faint set of lines for 50 ms, and your task is to report the angle of the lines. Sometimes the pattern appears on the left of the screen and sometimes on the right. The stimulus is adjusted so you are correct a little more than chance, but you often say you didn't see it at all. Now suppose that 400 ms *after* the stimulus, a cue flashes to tell you whether the stimulus was on the left or right of the screen. That stimulus increases both the chance you will say you saw the stimulus, and your accuracy of identifying its angle (Sergent et al., 2013). So you are capable of becoming conscious of something after it is gone. Your brain held it in reserve, capable of activating it after the fact.

Overall, what research on consciousness has established so far is this: When you are conscious of something, activity from a sensory area of the cortex spreads to much of the rest of the cortex and rebounds to magnify and prolong activity in the original area. Also, consciousness depends on reciprocal connections that compare and integrate several types of information. Is that the whole story? Suppose we build a machine that takes input and spreads it through its operating system and then rebounds it to magnify and prolong the original input. The machine also compares and integrates several types of information. Is our machine therefore conscious? Maybe so, but if not, then we are missing something. Does consciousness apply only to carbon-based systems? If so, why? Do neurons have special properties that enable consciousness? If so, what?

Oh, and good luck on answering those questions.

Stop & Check

24. In what way does the phi phenomenon imply that a new stimulus sometimes changes consciousness of what went before it?

See page 451 for the answer.

Inferring Overall Consciousness or Unconsciousness

We need to distinguish two questions about the physiology of consciousness. So far, we have focused on what happens when an alert person becomes conscious of a particular stimulus. The other question is what enables a person (or animal) to be aware of anything at all.

Inferring Consciousness in Humans

How do brains differ when people are conscious from when they are unconscious? This is not an altogether easy question for researchers, because we are not always certain whether someone is conscious. People sometimes respond to a stimulus without being conscious. People with blindsight respond to a visual stimulus while insisting that they did not see it. People can also be conscious without responding. When people are forced to awaken suddenly during anesthesia, they do not always report that they had been unconscious (Scheinin et al., 2021). Researchers make inferences about consciousness, but they cannot always be sure.

Studies have followed people as they lost consciousness under anesthesia and then regained it as the drug

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effects wore off. Loss of consciousness was marked by decreased overall activity, decreased dopamine input to parts of the cortex, and decreased connectivity between the thalamus and cortex (Långsjö et al., 2012; Schröter, 2012; Spindler et al., 2021). Recovery of consciousness depended on increased connectivity between subcortical and cortical areas, and then by increased activity in the cortex. Recall the earlier discussion that consciousness of a stimulus requires a spread of activity over much of the brain. With a loss of connectivity, no stimulus can spread its activity, and consciousness ceases.

People in an unresponsive wakefulness state alternate between sleep and wakefulness, but even when awake, they demonstrate no purposeful behaviors. Might they nevertheless be conscious? Researchers used fMRI to record brain activity in a young woman who was in a persistent unresponsive wakefulness state following brain injury from a traffic accident. She had neither spoken nor made any other purposive movements. However, when she was directed to imagine playing tennis, the fMRI indicated increased activity in motor areas of her cortex, like what healthy volunteers indicate after the same instruction. When she was told to imagine walking through her house, a different set of brain areas became active, again like the pattern for healthy volunteers (Owen et al., 2006). Follow-up studies found similar results in 4 of 53 patients in an unresponsive wakefulness state. One patient used brain activity—imagining tennis versus imagining walking through a house—to answer yes/no questions such as "Do you have a brother?" (Monti et al., 2010). This method does not always work. Some brain-damaged people who show signs of consciousness in other ways either do not understand the instructions, or cannot sufficiently imagine playing tennis, or lack the motivation to answer questions in this way.

Another approach requires no response at all. Researchers used brief magnetic stimulation to activate a localized brain area, and then used EEG to observe the spread of activity. The activity spread more widely for most people in a minimally conscious state than for people who were anesthetized or in NREM sleep (Casali et al., 2013; Rosanova et al., 2012). This method offers a potentially quick way to probe for consciousness in an unresponsive person.

Stop & Check

25. As people lost consciousness under anesthesia and later regained it, what changed most strikingly in the brain?

See page 451 for the answer.

Inferring Consciousness in Monkeys

You are aware of your own consciousness, but you can only infer it in others. People vary in their willingness to attribute consciousness. The extreme position is *solipsism*, the belief that "I alone am conscious." (Solipsists never organize mutual support groups. Every solipsist is convinced that all the other solipsists are wrong.) For those of us who are not solipsists, the question is to what other species, if any, shall we attribute consciousness.

Given the neurological similarities between humans and other species, there is no compelling reason to assume that only humans are conscious. Most people believe that their pet dog or cat is conscious, and if dogs and cats are, then probably other mammals also. When mice go from sleep to wakefulness, their brain activity changes in about the same way that human brains change when we gain consciousness (Gutierrez-Barragan et al., 2022). Birds also exhibit activities and responses that seem to imply conscious processing (Nieder et al., 2020). But where do we draw the line? What about reptiles and fish? Octopus? At least some insects and other invertebrates apparently feel pain, suggesting conscious experience (de Waal and Andrews, 2022).

For monkeys, researchers found a way to make consciousness an empirical question. Here is the task, and you can imagine doing it yourself: You stare at a screen, and you are supposed to press a key to guess whether a target is about to appear on the left or right side. On some trials, a symbol flashes briefly on the side *opposite* to where the target will appear. If it is present long enough for you to see it, you will almost always respond correctly, because the symbol cued the correct answer. At other times the symbol is present so briefly that you deny seeing anything, but this unconscious (subliminal) stimulus affects your behavior. On those trials, more often than not, you guess *incorrectly*. The unconscious stimulus drew your attention to one side, without cuing you consciously with information you could use. With rhesus monkeys, the results are the same. They learn to choose the side opposite to a symbol that appeared for 250 ms, but they usually choose the same side as a symbol that appeared for 17 or 33 ms (Ben-Haim et al., 2021). The monkeys demonstrate the same distinction between conscious and unconscious stimuli that people do.

Stop & Check

26. If the monkeys had chosen randomly after the symbol appeared for 17 or 33 ms, what conclusion would have followed?

See page 451 for the answer.

Attention

Attention isn't synonymous with consciousness, but it is closely related. Of all the information that strikes your eyes, ears, and other receptors, you are conscious of only those few to which you direct your attention (Huang et al., 2007). Consider **inattentional blindness** or *change blindness:* If something in a complex scene changes slowly, or

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changes while you blink your eyes, you probably will not notice it unless you were paying attention to the item that changed (Henderson and Hollingworth, 2003; Rensink et al., 1997).

Brain Areas Controlling Attention

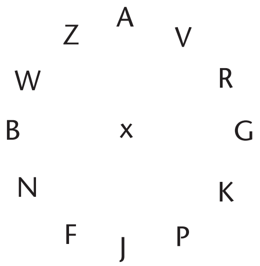
Psychologists distinguish bottom-up from top-down attention. A bottom-up process arises from a new stimulus. If you are sitting on a park bench when suddenly a deer runs past you, it grabs your attention. Top-down attention is intentional. If you are looking for someone in a crowd, you check one face after another.

Top-down attention depends on parts of the prefrontal and parietal cortex that facilitate responsiveness in thalamus, which in turn modifies responses in the primary sensory cortices (Chen et al., 2020; Engel et al., 2016; Wimmer et al., 2015). Neural responses to the attended stimuli increase and responses to other stimuli decrease (Bruckmaier et al., 2020; Poort et al., 2022).

The brain mechanisms for bottom-up attention overlap those for top-down attention. A sudden visual stimulus attracts your attention, and you look toward it. Tirin Moore and colleagues demonstrated that activating the neurons that would move your eyes toward something also increase attention in that direction. Artificially stimulating those neurons in the frontal cortex even slightly, not enough to evoke an eye movement, increases attention to the spot where the eyes would have moved, and therefore increases the ability to notice anything that appears there (Moore and Armstrong, 2003; Moore and Fallah, 2001).

You ordinarily perceive detail best in the fovea of your retina, but it is possible for you to direct your attention elsewhere in a top-down manner. To illustrate, keep your eyes fixated on the central *x* in the following display. Then attend to the *G* at the right and gradually shift your attention clockwise around the circle. Notice how you become aware of different parts of the circle without moving your eyes. As you deliberately shift your attention, you increase activity in one part after another of the visual cortex, including the neurons that would have moved your eyes one way or another (Kamitani and Tong, 2005; Wegener et al., 2004).

Try It Yourself



When a person is looking for something, they spread out their visual attention. In one experiment, people tried to locate a faint stimulus that could appear for just 250 milliseconds anywhere in a noisy field full of dots. They intentionally spread out their attention, and the result was that they were reasonably accurate throughout the visual field, but less accurate than usual in the foveal region. They increased their peripheral attention at the cost of foveal attention (Walshe and Geisler, 2022).

Another demonstration: What is the current sensation in your left foot? Chances are, before you read this question, you were not conscious of *any* sensation in your left foot. When you directed your top-down attention to it, activity increased in the corresponding part of the somatosensory cortex (Lambie and Marcel, 2002).

One of psychologists' favorite ways to study attention is the **Stroop effect**, the difficulty of ignoring words and saying the color of ink. In the following display, say aloud the color of ink of each word, ignoring the words themselves:

Try It Yourself

RED BLUE GREEN GREEN BROWN BLUE
RED PURPLE GREEN RED

After all your years of learning to read words, it is hard to suppress that habit and respond to the color instead. However, when people successfully do so, they enhance the activity in the color-vision areas of the cortex and decrease the activity in the areas responsible for identifying words (Polk et al., 2008).

Your ability to resist distraction fluctuates. Sometimes your "mind wanders," interfering with a task, especially a difficult one (Thomson et al., 2015). In one experiment, people's task was to find a circle within an

Tirin Moore

Tirin Moore (b. 1969)

Observing, or deducing, some previously unknown fact of nature is easily the most exhilarating experience one can have. (Moore, personal communication)

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array of squares. On some trials, one of the squares was red instead of green. Anything that is different attracts attention, and on the average, people found the circle more slowly on trials with a red square present. However, the speed of responding varied from trial to trial. On trials when activity was enhanced in the middle frontal gyrus (part of the prefrontal cortex) at the start of the trial (before seeing the stimuli), people did their best at ignoring the red square and thereby resisting distraction (Leber, 2010). This result confirms the importance of the prefrontal cortex in controlling attention.

Stop & Check

27. What evidence demonstrates a strong relationship between eye movements and visual attention?

See page 451 for the answer.

Spatial Neglect

Brain damage can impair attention in several ways. Many people with damage to the right hemisphere demonstrate **spatial neglect**—a tendency to ignore the left side of the body, the left side of objects, much of what they hear in the left ear, and much of what they feel in the left hand, especially in the presence of any competing sensation from the right side. Some people have been known to put clothes on only the right side of the body. These effects are most pronounced early after a stroke or other damage, and most people exhibit at least partial recovery over the next 10 to 20 weeks (Nijboer et al., 2013). Spatial neglect after left-hemisphere damage is less common.

If asked to point straight ahead, most patients with neglect point to the right of center. If shown a long horizontal line and asked to divide it in half, generally they pick a spot to the right of center, as if part of the left side wasn't there (Richard et al., 2004).

Some patients with neglect also exhibit deviations when estimating the midpoint of a numerical range. For example, what is halfway between 11 and 19? The correct answer is, of course, 15, but some people with neglect say "17." Evidently, they discount the lower numbers as if they were on the left side (Doricchi et al., 2005; Zorzi et al., 2002). In Western society, many people visualize the numbers as a line stretching to the right, as on the x-axis of a graph, and they also imagine time as moving from left to right. Researchers presented some made-up statements about the past and the future, and then tested how well people with spatial neglect remembered the statements. They forgot more statements about the past than about the future, again suggesting neglect of things imagined to be toward the left (Saj et al., 2014).

Although some neglect patients have sensory losses, in many cases, the main problem is loss of attention rather than impaired sensation. One patient was shown a letter E, composed of small H's. She identified it as a big E composed of small H's, indicating that she saw the whole figure. However, when she was then asked to cross off all the H's, she crossed off only the ones on the right. The researchers summarized by saying she saw the forest but only half the trees (Marshall and Halligan, 1995).

Several procedures increase attention to the neglected side. Simply telling the person to pay attention to the left side helps briefly. So does having the person look left while at the same time feeling something with the left hand (Vaishnavi et al., 2001) or hearing a sound from the left side of the world (Frassinetti et al., 2002).

Other manipulations also shift the attention. For example, some patients with neglect usually report feeling nothing with the left hand, especially if the right hand feels something at the time. However, if you cross one hand over the other as exhibited in Figure 13.15, the response increases for the left hand, which is now on the right side of the body (Aglioti et al., 1999). Also, the person ordinarily has trouble pointing to anything in the left visual field but has somewhat better success if the hand was so far to the left that the response would be to move the hand to the right to point to the object (Mattingley et al., 1998). Again, the conclusion is that neglect is not due to a loss of sensation but a difficulty in directing attention to the left side.

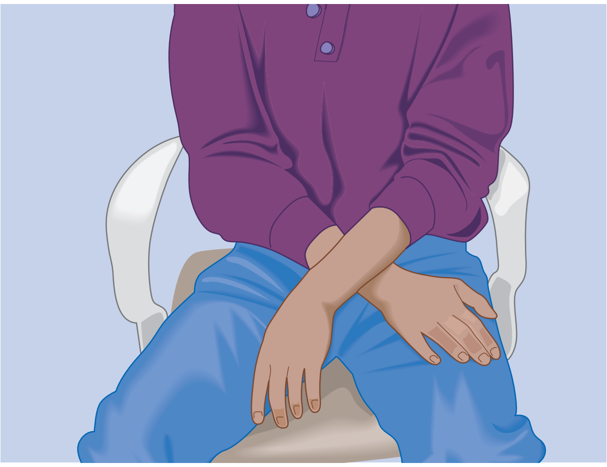
Stop & Check

28. What evidence indicates that spatial neglect is a problem of attention, not just sensation?

See page 451 for the answer.

Figure 13.15 A way to reduce sensory neglect

Ordinarily, someone with right hemisphere damage neglects the left arm. However, if the left arm crosses over or under the right, attention to the left arm increases.



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Module 13.2 | In Closing

Being Conscious of Consciousness

Consciousness is hard to explain. How do the neurons in the visual cortex "know" that the transmitters providing them with input came from visual stimuli? Why does the activity of those neurons, or of any neurons, constitute a visual experience, or any experience at all? In spite of the difficulties, at least consciousness has become a focus of serious biological research.

Summary

1. Dualism—the belief in a nonmaterial mind that exists separately from the body—conflicts with the conservation of matter and energy. Nearly all neuroscientists and philosophers accept some version of monism, the idea that mental activity is inseparable from brain activity. **441**
2. The hard problem is the question of why consciousness exists at all. **442**
3. Modern methods of measuring brain activity have made research on consciousness possible and respectable. Researchers present the same stimulus under conditions when an observer probably will or probably will not identify it consciously. **443**
4. When someone is conscious of a stimulus, the representation of that stimulus spreads over much of the brain and rebounds back to magnify and prolong processing in the primary sensory cortex. **443**
5. During binocular rivalry, the brain processes information from the ignored eye enough to recognize something that might be meaningful. **444**
6. Activity in the cerebellum is not conscious, although it has more neurons and synapses than the cerebral cortex. A key feature of the cerebral cortex is its reciprocal connections that compare and integrate different types of information. **445**
7. The phi phenomenon and others demonstrate that sometimes an event retroactively influences conscious perception of what came before it. **446**
8. People remain conscious only when the cortex receives enough stimulation from the thalamus and other subcortical areas. **446**
9. A few people diagnosed as being in an unresponsive wakefulness state have indicated consciousness, such as by brain responses when instructed to imagine playing tennis. **447**
10. Monkeys and humans demonstrate similar responses to signals that are presented at durations that do or do not enable conscious perception. **447**
11. Bottom-up attention occurs when a new stimulus arises. Mechanisms directing eye movements to a stimulus also direct attention toward it. **448**
12. Top-down attention occurs when the prefrontal cortex and parietal cortex facilitate responsiveness to some stimuli more than others. **448**
13. Spatial neglect results from a deficit in attention, not sensation. For example, someone with neglect can see an entire letter enough to say what it is, even though that same person ignores the left half when asked to cross out all the elements that compose it. **449**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

binocular rivalry	**444**
conscious	**443**
dualism	**441**
flash suppression	**443**
hard problem	**442**
identity position	**442**
inattentional blindness	**447**
masking	**443**
materialism	**442**
mentalism	**442**
mind–body or mind–brain problem	**441**
monism	**441**
phi phenomenon	**446**
spatial neglect	**449**
Stroop effect	**448**

Thought Question

What evidence, if any, would convince you that a computer or robot was conscious?

Stop & Check Answers

17. Dualism contradicts the law of the conservation of matter and energy. According to that law, the only way to influence matter and energy, including that of your body, is to act on it with other matter and energy.
18. The hard problem is why minds exist at all in a physical world. Why is there such a thing as consciousness?

19. Viewers were not conscious of a stimulus if it was preceded and followed by an interfering pattern.
20. A stimulus that reached consciousness activated the same initial brain areas as an unconscious stimulus but more strongly, spread to additional areas, and rebounded to magnify the initial response. Also, brain responses became synchronized.
21. Make one stimulus pulsate at a given rhythm and look for brain areas depicting that rhythm of activity. The rhythm takes over widespread areas of the brain when that pattern is conscious.
22. If a stimulus gradually appears on your ignored side, your attention shifts to it faster if the stimulus is meaningful to you.
23. The cortex has many reciprocal connections that enable areas to send messages and receive feedback.
24. Someone who sees a dot alternating left and right perceives the dot as moving. The viewer could not see the movement left to right until after the dot appeared on the right.
25. Connectivity among brain areas increased as people regained consciousness.
26. In that case we would see no evidence for unconscious processing in monkeys, and therefore no demonstrated distinction between conscious and unconscious. The experiment would have been inconclusive with regard to monkey consciousness.
27. Weakly stimulating cells that would have moved the eyes to a particular location increases attention to that location.
28. A patient with neglect who sees a large letter composed of small letters can identify the large letter but neglects part of it when asked to cross off the small letters. Also, someone who neglects the left hand pays attention to it when it is crossed over the right hand.

Module 13.2 | End-of-Module Quiz

1. The identity position regarding mind and brain endorses which of these statements?
   - **a.** The physical world cannot exist unless a mind is aware of it.
   - **b.** Mental activity causes brain activity.
   - **c.** Brain activity causes mental activity.
   - **d.** Mental activity and brain activity are the same thing.

2. What is the “hard problem”?
   - **a.** The question of why the cerebral cortex is conscious, and the cerebellum is not
   - **b.** The question of whether consciousness depends on the anterior or posterior cortex
   - **c.** The question of why consciousness exists at all
   - **d.** The question of how rapidly a sensory stimulus reaches consciousness

3. What do the following have in common: flash suppression, backward masking, and binocular rivalry?
   - **a.** They prevent consciousness of a stimulus that someone would otherwise perceive.
   - **b.** They measure the time required for a stimulus to reach consciousness.
   - **c.** They increase the spread of information to widespread areas of the cortex.
   - **d.** They improve someone’s ability to maintain attention despite distraction.

4. If your left eye views red vertical stripes and your right eye views green horizontal stripes, what do you perceive?
   - **a.** Red superimposed on green stripes
   - **b.** Yellow diagonal stripes
   - **c.** A white field without stripes
   - **d.** Alternation between seeing red stripes and green stripes

5. What happens when you are conscious of a stimulus that does not happen when the same stimulus is present while you are unconsciousness of it?
   - **a.** Rhythms of activity in the brain become more variable.
   - **b.** Activity increases in the pineal gland.
   - **c.** The response in the right hemisphere is greater than in the left.
   - **d.** The response to the stimulus spreads and strengthens.

6. What enables the cerebral cortex to be conscious, whereas the cerebellum is not?
   - **a.** The cerebral cortex has more total neurons.
   - **b.** The cerebral cortex has a greater variety of neurotransmitters.
   - **c.** The cerebral cortex has many reciprocal connections.
   - **d.** The cerebral cortex is closer to the eyes and ears.

7. What happens to enable an unconscious person to regain consciousness?
   - **a.** Development of synchrony between the left and right hemispheres
   - **b.** Increased growth of myelin sheaths
   - **c.** Longer, slower waves on the EEG
   - **d.** Increased input from the thalamus and other subcortical areas

8. Certain people in an unresponsive wakefulness state indicated consciousness by what?
   - **a.** Laughing or crying in response to what someone said
   - **b.** Moving their eyes to the left or right to answer yes/no questions
   - **c.** Different brain activity after directions to imagine certain activities
   - **d.** Squeezing the hand of a loved one while ignoring the hands of unfamiliar people

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9. What empirical evidence supports the inference of conscious experience in monkeys?

- **a.** They demonstrate both short-term and long-term memory.
- **b.** Their brains have the same neurotransmitters that humans have.
- **c.** Their brain waves during REM and NREM sleep resemble those of humans.
- **d.** They respond as humans do to supraliminal and subliminal visual stimuli.

10. What is meant by "inattentional blindness"?

- **a.** The correlation between attention deficit disorder and visual problems
- **b.** The difficulty of naming the colors of words while ignoring their meanings
- **c.** The tendency to ignore changes in anything not attended to
- **d.** The decreased activity of the visual cortex while listening to music

11. Suppose someone who is trying to divide a horizontal line in half picks a spot far to the right of center. This result suggests probable damage or malfunction in which part of the brain?

- **a.** The left hemisphere
- **b.** The right hemisphere
- **c.** The prefrontal cortex
- **d.** The primary visual cortex

Answers: 1d, 2c, 3a, 4d, 5d, 6c, 7d, 8c, 9d, 10c, 11b.

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Module 13.3

Making Decisions and Social Neuroscience

Learning Objectives

After studying this module, you should be able to:

14. Describe research on the brain mechanisms of perceptual decisions.
15. Describe research on the brain mechanisms of value decisions.
16. List key findings about biological influences on social behavior.

Life is full of decisions. Some are big ones: Where should I go to college? What kind of job should I seek? Some are small ones: Should I wear the green shirt or the blue one today? What kind of sandwich do I want for lunch? In each case, you consider the pluses and minuses.

Human life is also full of social interactions. Cooperation enhances our opportunities. Tonight you might drive a car made in Europe and powered by fuel from the Middle East so you can eat food grown in Asia, cooked from a recipe from South America, at a restaurant built by people in a previous century. And you are protected from disease by the efforts of medical researchers from many countries and many centuries.

In this module, we consider your brain activity during decision making and social behavior. These topics are not closely related, but we consider them together just because the treatment of each topic is short. Research on both topics began more recently than for the rest of neuroscience, and the conclusions are tentative.

Decisions

One type of decision is factual: Do these glasses improve my vision more than those do? Is the meal that I am cooking ready to come out of the oven, or not? To answer such questions, you weigh the evidence. Another type of decision is one of values: Would I prefer this choice or that one? Decision making is hard to study. Researchers almost always simplify the situation to a single choice between just two options (Mattar and Lengyel, 2022).

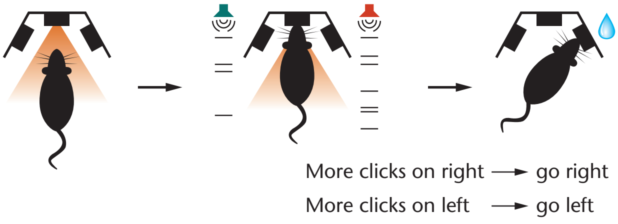
Factual Decisions

When you make a decision about factual matters, one set of cells accumulates evidence in favor of one choice, another set accumulates evidence for another choice, and a third set compares the two. In one study, a rat had to put its nose into a central port, listen to clicks, and then turn to the side with more clicks. The rat had to decide, do I hear more clicks on the left or on the right? Figure 13.16 depicts the setup. One set of cells in the posterior parietal cortex responded in proportion to the clicks on the left, and another set responded in proportion to the clicks on the right. Those cells fed information to the prefrontal cortex, which compared the two (Yao et al., 2020; Zhao and Freedman, 2019). Whereas cells in the posterior parietal cortex responded in proportion to the number of clicks, responses in the frontal cortex produced an all-or-none outcome, like a scorekeeper who announces which team won the game, regardless of whether the score was close or lopsided. One set of cortical cells responded when the left side was ahead, and another set responded when the right side was ahead (Hanks et al., 2015). After damage to the prefrontal cortex, a rat could not keep track of the score, and it decided based on the last clicks it heard (Erlich et al., 2015). Other studies confirmed that certain neurons in the prefrontal cortex, specifically the dorsolateral part of the prefrontal cortex, act as the "scorekeeper" (Lin et al., 2020; Zatka-Haas et al., 2021).

In a similar type of study, a monkey gazed at a fixation point and responded with a left or right eye

Figure 13.16 Design for a study of decision making in rats

If the rat heard more clicks on the left side, it can turn left for reward. If it heard more on the right side, it can turn right for reward.


More clicks on right → go right
More clicks on left → go left

movement based on whether it saw dots moving mostly left or right. The task is more difficult than it sounds, because only a few dots were moving, and a larger number of dots were appearing and then disappearing at random positions on the screen. The monkey watched for a while, and then had to wait a few seconds before responding. Within the parietal cortex, one set of cells responded whenever most of the dots moved left, and a different set responded when the dots moved right. During the delay before the monkey could respond, the relative response of the two types of cells shifted more and more strongly in one direction. If the "look left" cells were a little ahead of the "look right" cells at the start of the delay, they became more and more ahead as time passed, suggesting that the monkey became more committed to the decision.

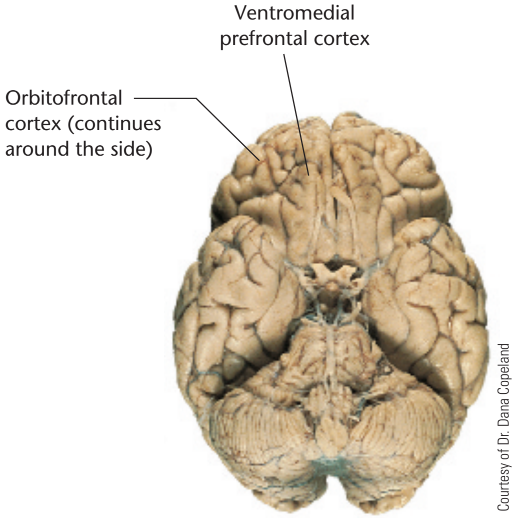
Stop & Check

29. When a rat is deciding whether it hears more clicks on the left or right side, what happens in the prefrontal cortex?

See page 457 for the answer.

Figure 13.17 Two areas of the prefrontal cortex

The ventromedial prefrontal cortex and the orbitofrontal cortex are important contributors to decisions.


Ventromedial prefrontal cortex
Orbitofrontal cortex (continues around the side)

Courtesy of Dr. Dana Copeland

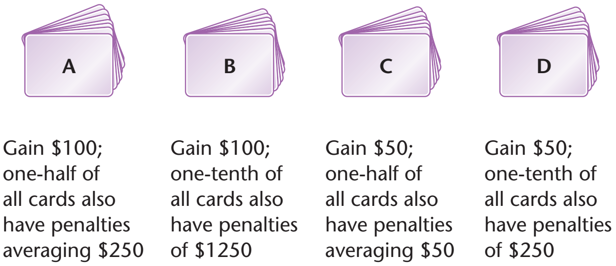
Value Decisions

When you make a decision based on preferences, you estimate the probable outcome of each choice, and weigh which outcome seems better. Suppose one choice always yields a moderate reward, but a risky choice sometimes yields a huge reward and usually yields little, nothing, or even a penalty. The animal has to learn probabilistically over many trials, relying mainly on cells in the basal ganglia. Cells in the **ventromedial prefrontal cortex** also participate, by rapidly learning new information. If the basal ganglia gradually learned that choice A is usually better than B, but something now favors choice B, the rapid-learning prefrontal cortex can overrule the slower-learning basal ganglia (Brigman et al., 2013; Kovach et al., 2012).

Suppose you have an opportunity to bet at a roulette wheel, and you are permitted only to bet on red, but you can vary the amount you bet. As a complication, the number of red slots varies from time to time. (Okay, it's a weird roulette wheel.) You would, of course, bet more heavily on red when you see more red slots. Most people with damage to the prefrontal cortex tend to bet about the same amount each time, based on their average expectation (Manohar and Husain, 2016; Struder et al., 2015). Their basal ganglia learn what usually happens, and they fail to update based on current information.

The **orbitofrontal cortex** (Figure 13.17) has multiple functions in decision making that are not easy to summarize. It learns rules about the environment, such as that if one fruit on a tree is ripe, the others probably are also (Klein-Flügge et al., 2022; Knudsen and Wallis, 2022). Another function is that compares an expected reward to other possible choices (Murray and Rudebeck, 2018). Getting a B+ on your term paper might be delightful or disappointing, depending on what you had been expecting. In one study, monkeys could choose between two juices by moving their eyes left or right. On a given trial the choice might be between one drop of apple juice or one drop of peppermint tea, or between one drop of apple juice and three drops of cranberry juice. Many orbitofrontal cells changed their responses to a stimulus depending on the other choice. A cell might respond strongly to the apple juice when it was the preferred choice but not so much when a better choice was available (Xie and Padoa-Schioppa, 2016). In a similar study, if a monkey had a choice between rewards of almost equal value, its orbitofrontal neurons flipped back and forth between two patterns of activity, apparently because the monkey having trouble deciding (Rich and Wallis, 2016).

Impairment or relative inactivity in the orbitofrontal cortex in humans is often associated with poor or impulsive decisions. Consider the Iowa Gambling Task:


A
B
C
D
Gain $100; one-half of all cards also have penalties averaging $250
Gain $100; one-tenth of all cards also have penalties of $1250
Gain $50; one-half of all cards also have penalties averaging $50
Gain $50; one-tenth of all cards also have penalties of $250

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People can draw one card at a time from four piles. They can always win $100 in play money by playing from decks A or B, or $50 from C or D. However, some cards also have penalties:

When you examine the payoffs, you can see that the best strategy is to pick cards from decks C and D. In the experiment, however, people had to discover the payoffs by trial and error. Ordinarily, as they sampled from all four decks, they gradually started exhibiting signs of tension whenever they drew a card from A or B, and they shifted their preference toward C and D. People with damage to the orbitofrontal cortex and surrounding areas also preferred C and D if their first few choices from A and B hit them with penalties. However, if they started with a streak of wins from A and B, they were slow to switch (Stalnaker et al., 2015). Again, the point is that the prefrontal cortex updates the relative advantage or disadvantage of each possible choice.

Stop & Check

30. How does the role of the prefrontal cortex differ from that of the basal ganglia?
31. What is the role of the orbitofrontal cortex in decision making?

See page 457 for the answer.

Individual Differences

Some people make better decisions than others, and everyone makes better decisions at some times than others. Why? There can be any number of reasons, but they include some that we might not immediately think of. One is heart rate variability. The vagus nerve, part of the parasympathetic nervous system, controls heart rate. People with greater heart rate variability from moment to moment tend to make better decisions, especially in situations of risk and uncertainty such as the Iowa Gambling Task (Forte et al., 2022). The explanation is not known, but one possibility is that changes in vagus activity indicate increased mental effort. Note that we are talking about variability in heart rate, not blood pressure. Fluctuating blood pressure is a risk factor for cognitive decline in old age (de Heus et al., 2021).

Here is another influence on decision making that we might not think of: The bacteria in the digestive system. People have a great variety of bacteria in the gut, mostly performing important functions such as breaking down proteins so that they can be absorbed, producing short-chain fatty acids, and helping with immunity against harmful substances. However, some types of intestinal bacteria produce inflammation, impair cognition, and increase the risk of psychological and neurological disorders (Suganya and Koo, 2020). When people say they made a bad decision based on a "gut feeling," it might be literally true.

The Biology of Love

Social neuroscience, the study of how genes, chemicals, and brain areas contribute to social behavior, is a relatively new area of study. We shall consider two topics, love and altruism.

Suppose you are passionately in love with someone. According to studies using fMRI, looking at pictures of the person you love strongly activates the brain areas associated with reward, in ways resembling the effects of addictive drugs (Burkett and Young, 2012). Viewing photos of your beloved also activates the hippocampus and other areas important for memory and cognition, as you remember what you have done together (Ortigue et al., 2010). The point is that what we call love combines motivations, emotions, memories, and cognitions.

The role of **oxytocin** and the closely related hormone vasopressin has attracted much attention. Oxytocin stimulates contractions of the uterus during childbirth, stimulates breasts to produce milk, and promotes maternal behavior, social approach, and pair bonding in many mammalian species (Marlin et al., 2015; McCall and Singer, 2012; Sobota et al., 2015). Both men and women release it during sexual activity. Much research has investigated its possible ability to intensify love relationships.

A common way to study oxytocin's effects has been to give it as a nasal spray and compare its effects to a placebo. Here are some of the reported effects:

- Oxytocin increased men's ratings of the attractiveness of their female partners, without changing their ratings of other women (Scheele et al., 2013).
- When young men who were in a monogamous relationship with a woman met another attractive woman, oxytocin caused them to stand farther away than other men did, apparently because oxytocin had enhanced fidelity to their partners (Scheele et al., 2012).
- Oxytocin improved facial recognition by people who were ordinarily less skilled at this ability (Bate et al., 2014; Guastella et al., 2010).
- Oxytocin increased conformity to the opinions of people's in-group, but not to those of unfamiliar people (Stallen et al., 2012).
- Oxytocin increased trust toward in-group members, but had variable effects on trusting other people (van Ijzendoorn and Bakermans-Kranenburg, 2012).
- Oxytocin increased attention to possible dangers when people saw themselves as threatened (Olff et al., 2013; Poulin et al., 2012).

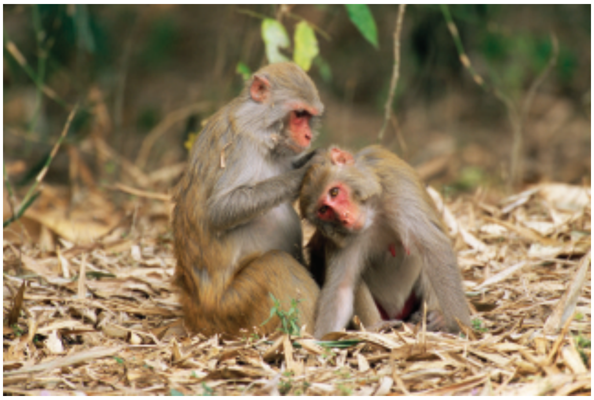
These studies imply that oxytocin increases attention to social cues and intensifies existing relationships. Unfortunately, the evidence is not as strong as we would hope. Although oxytocin in a nasal spray can reach the brain, probably not much of it does, and it arrives more slowly than the duration of most experiments. Furthermore, most studies have used only small numbers of participants, and several results have been difficult to replicate (Mierop et al., 2020). The studies have been "under-powered" in the statistical sense—that is, unable to reliably detect an effect of the expected size. The hypothesis that oxytocin enhances social attention and loving relationships may well be true, but the evidence so far is not convincing.

Social Interactions

Civilized life depends on people helping one another. You help people near you who seem to be in trouble, and you might contribute money to help victims of a natural disaster on the other side of the world. Animals other than humans also display concern about others of their species, especially familiar ones. Just as you might hug someone who seems unhappy, monkeys groom others that have been hurt (Figure 13.18). Mice groom one another, too, responding to olfactory cues that indicate distress (Wu et al., 2021).

As in humans, monkeys help some partners more than others. In one study, rhesus monkeys could offer food. They reciprocated with monkeys who had offered them food in the past, but not those that had previously failed to offer. Neurons in the dorsomedial prefrontal cortex responded specifically to different monkeys, depending on how they had acted in the past. Disrupting those neurons left the monkeys responding unselectively, treating equally those that had or had not been helpful in the past (Báez-Mendoza et al., 2021). Evidently those neurons are important for social behaviors. Neurons in the hippocampus and amygdala are also necessary for recognizing other individuals and establishing relationships with them (Lopez-Rojas et al., 2022; Pryluk et al., 2021; Terranova et al., 2022).

Figure 13.18 Mutual grooming is important for maintaining social relationships in monkeys.



James Warwick/The Image Bank/Getty Images

In another study of monkeys, fMRI located a network of neurons in the prefrontal cortex that respond strongly to videos of social behaviors of other monkeys. Those neurons were in the areas of the human brain reportedly important for "theory of mind," the ability to imagine what other people probably know or believe (Sliwa and Freiwald, 2017). The prefrontal areas important for social behavior may not be devoted exclusively to social stimuli. Researchers found similar results in the fMRI results for people playing a game against another person or playing a similar game against a computer program (Konavalov et al., 2021). One might argue, of course, that people react to a computer as if it were another person.

Most people are more generous toward people similar to themselves. For example, if you watch someone who is feeling socially rejected by others, you will "feel the pain" and your brain will react accordingly, but you react more strongly if that person is one of your relatives or friends (Beeney et al., 2011). Some people express more empathy than others do, largely because of culture and family upbringing, but also because of biological factors. The most profound deficit occurs in a condition called **frontotemporal dementia**, in which parts of the frontal and temporal lobes of the cerebral cortex gradually degenerate. The damage usually includes the ventromedial prefrontal cortex and orbitofrontal cortex, which are important for evaluating possible rewards and also for interpreting other people's emotional expressions (Delgado et al., 2016; Jenkins et al., 2014). Some of the people with damage of this type do not recognize or respond to other people's distress reactions (Oliver et al., 2015; Van den Stock et al., 2015). As mentioned in the emotion chapter, people with damage in the ventromedial prefrontal cortex are more likely than others to calmly endorse a utilitarian moral position that it would be okay to kill one person to save five.

People with frontotemporal dementia also exhibit little interest in how others perceive them. Suppose an experimenter asks you to sing, karaoke-style, in a room by yourself, but secretly videotapes your performance and then shows it to you while other people are watching. Unless you are a fine singer, you will presumably feel embarrassed. In contrast, people with frontotemporal dementia seem quite calm, even if their singing is dismally bad (Sturm et al., 2008).

Stop & Check

32. What is the current status of oxytocin as a contributor to loving relationships?
33. Which brain areas are important for value decisions and also for understanding other people's emotional expressions?

See page 457 for the answer.

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Module 13.3 | In Closing

Biology of Decisions and Social Behavior

You may have noticed that this was a short module. Why do neuroscientists have so much more to say about vision, for example, than about decisions or social behavior? The reason has nothing to do with a lack of interest. The reason is that researchers prefer questions that they know how to answer. With vision or other senses, they can control the stimuli precisely and measure responses with reasonable accuracy. Decision making and social behavior are complicated. The effort to understand them biologically is in the early stages, but at least it has begun.

Summary

1. In a perceptual decision, neurons in the parietal cortex respond in proportion to evidence favoring one choice or the other, and cells in the prefrontal cortex compare them to determine which choice has the stronger support. **453**
2. Cells in the basal ganglia gradually learn which choice is better, but cells in the ventromedial prefrontal cortex can overrule the basal ganglia based on a recent change in the situation. **454**
3. People with damage to the prefrontal cortex tend to follow habits instead of updating their decisions based on current information. **454**
4. The orbitofrontal cortex evaluates each possible choice relative to the value of other available choices. **454**
5. People with damage to the prefrontal cortex are slow to switch strategies in situations such as the Iowa Gambling Task. **455**
6. Passionate love excites the brain in ways that resemble those of addictive drugs. **455**
7. Many studies have reported that the hormone oxytocin increases attention to social stimuli and intensifies social relationships. However, although that conclusion may be correct, much of the evidence so far has been weak. **455**
8. Neurons in the prefrontal cortex respond to others' social behaviors and influence behavior toward others who have or have not been cooperative in the past. **456**
9. People with frontotemporal dementia have difficulty with understanding others' emotions, and respond only weakly to others' distress. **456**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

frontotemporal dementia	**456**
orbitofrontal cortex	**454**
oxytocin	**455**
social neuroscience	**455**
ventromedial prefrontal cortex	**454**

Thought Question

What would you predict about the brain reactions of people with psychopathic traits?

Stop & Check Answers

29. Depending on which ear is ahead at a given point, one set of cells or another one becomes active.

30. The basal ganglia gradually learn a preference based on the usual results. The prefrontal cortex modifies a preference based on the most recent information.

31. The orbitofrontal cortex evaluates each choice in comparison to others that are available.

32. Many studies suggest that oxytocin magnifies attention to social cues and intensifies relationships, but much of the research has been weak.

33. The ventromedial prefrontal cortex and the orbitofrontal cortex.

Module 13.3 | End-of-Module Quiz

1. During a factual decision, which brain area acts as the "scorekeeper"?
   - **a.** Amygdala
   - **b.** Parietal cortex
   - **c.** Prefrontal cortex
   - **d.** Hippocampus

2. In a value decision, how do responses by the ventromedial prefrontal cortex differ from those of the basal ganglia?
   - **a.** The ventromedial prefrontal cortex excites, whereas the basal ganglia inhibit.

b. The ventromedial prefrontal cortex monitors the average over many trials.
c. The ventromedial prefrontal cortex adjusts more rapidly to new information.
d. The ventromedial prefrontal cortex is more sensitive to rewards than punishments.

3. How would decision making change as a result of prefrontal cortex damage?

a. Prolonged delay before making any decision
b. Extreme caution to avoid possible losses
c. Decisions based on habits more than current information
d. Random guessing

4. Why are many neuroscientists skeptical of the reported social effects of oxytocin?

a. The human brain does not produce oxytocin.
b. The results in the United States differ from those of people in other parts of the world.
c. Artificial administration of oxytocin produces only a brief change in behavior.
d. Most of the studies used small numbers of participants.

5. How did monkeys respond after impairment of the dorsomedial prefrontal cortex?

a. They avoided all contact with other monkeys.
b. They paid more attention to other monkeys' recent behavior than their past pattern.
c. They paid more attention to other monkeys' hand gestures than facial expressions.
d. They failed to distinguish between monkeys that had or had not been cooperative.

Answers: 1c, 2c, 3c, 4d, 5d.

Suggestions for Further Reading

Dehaene, S. (2016). *Consciousness and the brain*. (Viking Press). Excellent review of research on how the brain's response differs between stimuli perceived consciously and those not perceived consciously.

Massimini, M., and Tononi, G. (2013). *Sizing up consciousness.* (Oxford University Press.) Clear and thoughtful discussion of what features of brain activity differentiate consciousness from unconsciousness.

Ornstein, R. (1997). *The right mind.* (Harcourt Brace). Clear description of split-brain research and the differences between the left and right hemispheres.

Chapter 14

It’s complicated: Many people who fit a diagnosis for one mental disorder may partially fit the diagnosis for another as well; other people may not completely match any specific diagnosis.

(Andrzej Dudzinski/Science Source)

Psychopathology

Chapter Outline

Module 14.1

Substance Abuse
Drug Effects
Predispositions
Treatments
In Closing: The Psychology and Biology of Substance Abuse

Module 14.2

Mood Disorders
Major Depressive Disorder
Antidepressant Drugs
Bipolar Disorder
In Closing: The Biology of Mood Swings

Module 14.3

Schizophrenia
Diagnosis
Genetic Influences
Environmental Influences
Brain Abnormalities
Treatments
In Closing: Many Remaining Mysteries

Module 14.4

Autism Spectrum Disorder
Symptoms and Characteristics
Genetics and Other Causes
Brain and Sensation
Treatments
In Closing: A Complex Disorder

Learning Objectives

After studying this chapter, you should be able to:

1. Describe the importance of dopamine and the nucleus accumbens in reward and addiction.
2. Discuss cravings and other explanations for habitual drug use.
3. Describe the role of genetics in substance abuse.
4. Describe genetic and environmental predispositions to alcohol abuse and other drug abuse.
5. Discuss possible treatments.
6. Describe the symptoms and characteristics of major depression.
7. Discuss the genetic and environmental predispositions toward depression.
8. Describe and evaluate the standard antidepressant drugs and the available alternatives.
9. Describe bipolar disorder and its treatment.
10. List the symptoms of schizophrenia, distinguishing between positive and negative symptoms.
11. Describe and evaluate the research on genetic predispositions to schizophrenia.
12. Discuss the environmental contributors and the two-hit hypothesis.
13. Discuss the treatments for schizophrenia and their limitations.
14. Describe the symptoms of autism, noting the variance among individuals.
15. Describe the genetic and environmental contributors.
16. Explain why some children with autism behave more normally when they have a fever.

Psychopathology is a widespread problem. Because it usually begins early in life, it causes more loss of productive and happy years of life than any other type of illness does. And yet most people with psychological problems fail to get effective treatment, either because it is not readily available, or because they resist treatment that carries with it a stigma (Insel, 2022).

Psychological disorders are unlike anything else that is considered part of medicine. A physician who wants to treat your cough will start by diagnosing whether you have influenza, a cold, an allergy, lung cancer, tuberculosis, or something else. A lab test can establish the diagnosis, which will guide the treatment. At one time, psychologists and psychiatrists were optimistic about a similar approach for mental illness, but research failed to support that approach. Any mental illness comes in degrees, and the borderline between "having" it or "not having" it is arbitrary. Also, many if not most people with psychological problems partly fit the diagnosis for several disorders without exactly fitting it for any of them. Most of them also have physical illnesses that contribute to their problems (Hagerty et al., 2019). The genes that predispose someone to one psychological disorder largely overlap the genes that predispose to others (Cross-Disorder Group, 2019). The characteristic proteins, immune responses, and epigenetic changes overlap for schizophrenia, bipolar disorder, and major depression (Network and Pathway Analysis Subgroup, 2015). Often a drug intended for the treatment of one diagnosis helps patients with other diagnoses.

In short, the categorical approach to mental illness is not quite right. This chapter is arranged around traditional categories, mainly because most of the research has dealt with a category, such as depression or schizophrenia. In defense of this organization, the categorical approach, though not quite right, is also not entirely wrong. Enough people have a primary difficulty of substance abuse, depression, or schizophrenia to justify research. Still, bear in mind that much that pertains to one disorder also pertains to other ones.

Module 14.1

Substance Abuse

Learning Objectives

After studying this module, you should be able to:

1. Describe the importance of dopamine and the nucleus accumbens in reward and addiction.
2. Discuss cravings and other explanations for habitual drug use.
3. Describe the role of genetics in substance abuse.
4. Describe genetic and environmental predispositions to alcohol abuse and other drug abuse.
5. Discuss possible treatments.

Drug abuse is a major health problem. At one point, it was widely believed that prescription opiates for pain relief were unlikely to be addictive. The resulting increase in prescriptions led to such widespread abuse that it qualifies as an epidemic. When fentanyl, a potent synthetic drug similar to morphine, became available, the result was a huge number of overdose deaths. Alcohol abuse has been a major health problem for centuries.

If you were doing something that did you more harm than good, you would stop doing it, right? That is why addictive behaviors are such a paradox. No one decides to become addicted. As an addiction progresses, the pleasures become weaker while the costs and risks increase.

Drug Effects

Let's start with a brief description of how drugs work. Most of the commonly abused drugs derive from plants. Nicotine comes from tobacco, caffeine from coffee and tea, opiates from poppies, and cocaine from coca. We might wonder why our brains respond to plant chemicals. An explanation is more apparent if we put it the other way: Why do plants produce chemicals that affect our brains? Nearly all neurotransmitters and hormones are the same in humans as in other species. So, if a plant evolves a chemical to attract bees, repel caterpillars, or whatever, that chemical is likely to affect humans also.

Drugs either facilitate or inhibit transmission at synapses. A drug that blocks a neurotransmitter is an **antagonist**, whereas a drug that mimics or increases the effects is an **agonist**. (The term *agonist* is derived from a Greek word meaning "contestant." The term *agony* derives from the same root. An *antagonist* is an "anti-agonist," or member of the opposing team.) A *mixed agonist–antagonist* is an agonist for some effects and an antagonist for others, or an agonist at some doses and an antagonist at others.

Investigators say that a drug has an **affinity** for a receptor if it binds to it, like a key into a lock. A drug's **efficacy** is its tendency to activate the receptor. A drug that binds to a receptor but fails to stimulate it has affinity but not efficacy.

The effectiveness and side effects of any drug vary from one person to another, because drugs affect several kinds of receptors. One person might have more dopamine type D$_4$ receptors and fewer D$_1$ or D$_2$ receptors, whereas someone else has the reverse (Cravchik and Goldman, 2000).

Stop & Check

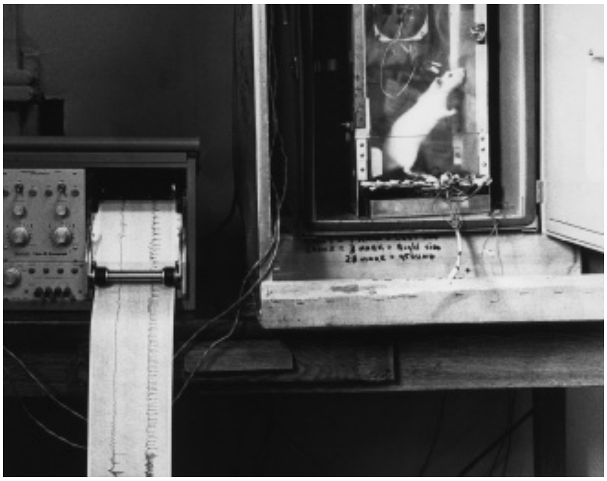
1. Is a drug with high affinity and low efficacy an agonist or an antagonist?

See page 468 for the answer.

The Role of Dopamine

When a pair of young psychologists were trying to answer an unrelated question, their accidental findings led to the discovery of the importance of dopamine in motivation. James Olds and Peter Milner (1954) wanted to test whether stimulation of a certain brain area might influence which direction a rat turns. When they implanted their electrode, they missed the intended target and instead hit an area called the septum. To their surprise, when the rat received the brain stimulation, it sat up, looked around, and sniffed, as if reacting to a favorable stimulus. Olds and Milner then gave rats the opportunity to press a lever to produce electrical **self-stimulation of the brain** (Figure 14.1). For stimulation of the septum or certain other places, rats pressed as often as 2,000 times per hour (Olds, 1958). Later researchers found that reinforcing stimulation directly or indirectly increases the release of dopamine in the **nucleus accumbens**, as illustrated in Figure 14.2 (Wise, 1996).

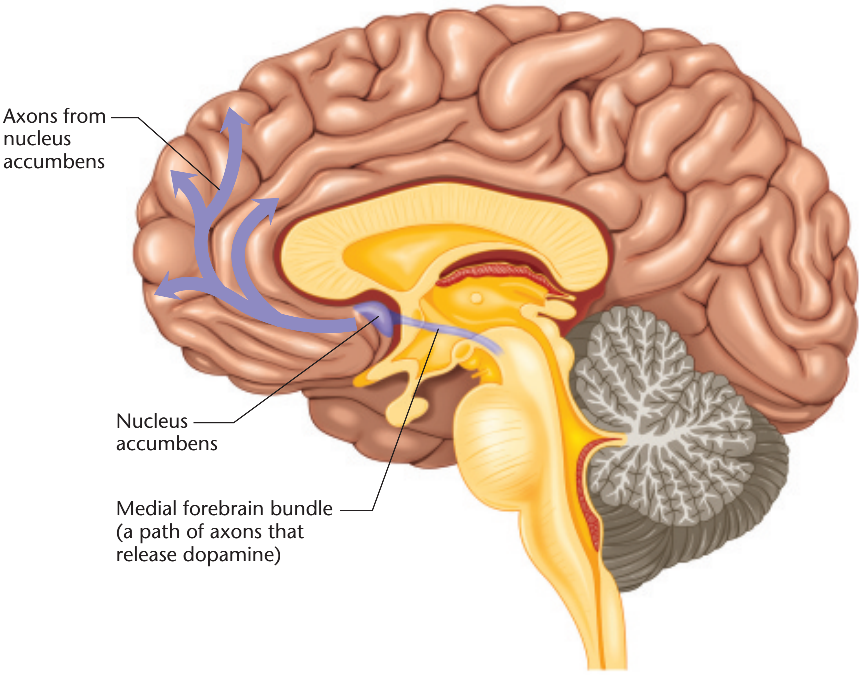
Figure 14.1 A rat pressing a lever for self-stimulation of its brain



Science Source

Figure 14.2 The nucleus accumbens in the human brain

Many abused drugs and other reinforcing activities increase dopamine release in the nucleus accumbens.


Axons from nucleus accumbens
Nucleus accumbens
Medial forebrain bundle (a path of axons that release dopamine)

(**Source:** © Cengage Learning 2013)

Stimulant drugs such as cocaine and amphetamine increase or prolong the release of dopamine in the nucleus accumbens (Calipari and Ferris, 2013). Nicotine stimulates neurons that release dopamine (Levin and Rose, 1995; Pontieri et al., 1996), and opiates inhibit neurons that inhibit dopamine release. Sexual excitement also releases

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dopamine in the nucleus accumbens (Damsma et al., 1992; Lorrain et al., 1999), along with music (Salimpoor et al., 2013), the taste of sugar (Roitman et al., 2008), and simply imagining something pleasant (Costa et al., 2010). Gambling activates this area for habitual gamblers (Breiter et al., 2001), and videogame playing activates it for habitual videogame players (Ko et al., 2009; Koepp et al., 1998).

Although it seems natural to assume from all this that dopamine mediates pleasure, much research makes that idea seem uncertain (Berridge and Kringelbach, 2015). Psychologists distinguish between *liking* and *wanting*. You might like a fattening dessert without wanting it, and you might want a medicine without liking it. Dopamine is important for the motivation to get something (wanting), but not necessarily for enjoying it. People with decreased dopamine, such as Parkinson's disease patients, can still enjoy a tasty treat, apparently as much as ever. Opioid transmission may be more important for the pleasure (Castro et al., 2021).

Stop & Check

2. What do drug use, sex, gambling, and videogame playing have in common?

See page 468 for the answer.

Cravings

A defining feature of addiction is **craving**, an insistent search. Even after prolonged abstinence, cues associated with the habit trigger a renewed craving. Seeing a lit cigarette triggers a craving in smokers (Hutchison et al., 2002), a video of cocaine use triggers cravings in cocaine users (Volkow et al., 2006), and the sight of a videogame triggers craving in an excessive videogame player (Thalemann et al., 2007). Most people who become addicted to a substance do not enjoy the experience as much as before, but they continue to want it (Bechara et al., 2019). They crave it.

Cravings are persistent because of changes in the brain. As Nora Volkow and others have demonstrated, after people become addicted to a drug, the drug releases less dopamine, but cues associated with the drug release more (Volkow et al., 2011; Volkow et al., 2019). Even after a long period of abstinence, the cues continue to grab attention and trigger a craving. Repeated drug use also makes the nucleus accumbens less responsive to other types of motivation. Cues for the drug attract even more attention because of the decreased competition (Epping-Jordan et al., 1998; Volkow et al., 2016; Wolf, 2016).

During a period of abstinence, the nucleus accumbens synapses responding to drug cues become even more sensitive for a while, before partly declining later. These results match indications that craving increases during the early stage of abstinence, and slightly declines later (Parvaz et al., 2016; Scheyer et al., 2016). Repeated alcohol or cocaine use also decreases blood flow and metabolism in the prefrontal cortex, resulting in decreased ability to restrain impulses (Du et al., 2020; Volkow et al., 1993, 1994).

Stop & Check

3. How does drug addiction modify the nucleus accumbens?
4. How do these changes help explain why someone who has abstained from an addiction might have a relapse?

See page 468 for the answer.

Tolerance and Withdrawal

As an addiction develops, many of its effects decrease. That decrease is called **tolerance**. Because of tolerance, heroin users raise their amount and frequency of use to greater and greater levels, eventually taking amounts that could kill other people. Drug tolerance is, to a large extent, learned. For example, rats that consistently receive a drug in a distinctive location show more tolerance there than elsewhere (Cepeda-Benito et al., 2005; Siegel, 1983). Cues associated with receiving the drug activate learned mechanisms that counteract the effects of the drug. Because tolerance is learned, it can be weakened through extinction procedures. After many injections of morphine, a rat develops tolerance to it. If the rat then receives repeated injections of salt water without morphine, it weakens its learned connection between injection and morphine. The result is decreased tolerance the next time it receives a morphine injection (Siegel, 1977).

As the body comes to expect the drug, it reacts strongly when the drug is absent. That reaction is called **withdrawal**. The withdrawal symptoms after someone quits heroin or other opiates include anxiety, sweating, vomiting, and diarrhea. Symptoms of alcohol withdrawal include irritability, fatigue, shaking, sweating, and nausea.

Nora Volkow

Nora Volkow (b. 1956)

Brain imaging and, particularly, molecular imaging… enable us to investigate how drugs including opioids interact with the brain and how they influence multiple signaling circuits. Brain imaging has shown that addiction is a disease of the brain—that it modifies specific areas of the brain in ways that help explain why some people are unable to stop taking a drug despite knowing the high price they are likely to pay. (Volkow & Czernin, 2019, p. 717, modified by personal communication)

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Efforts to avoid withdrawal symptoms contribute to addictive behaviors, but they are generally a minor contributor. Cocaine is addictive even though the withdrawal symptoms are mild. Gambling can be a powerful addiction, even though no substance is withdrawn.

Drug Use for Stress Reduction

One reason for an addiction is that a user learns to use the substance (or gambling habit or other addiction) to cope with stress. Researchers gave rats an opportunity to press a lever to inject themselves with heroin. Then they removed the lever. Midway through the withdrawal period, some of the rats had an opportunity to self-administer heroin again, while others went through withdrawal without heroin. Later, when rats went through withdrawal a second time, all the rats had an opportunity to press a lever to try to get heroin, but this time, the lever was inoperative. Although both groups of rats pressed the lever, those that had self-administered heroin during the previous withdrawal state pressed more frequently (Hutcheson et al., 2001). Evidently, receiving an addictive drug during a withdrawal period is a powerful experience. Users—rat or human—learn that the drug relieves the distress caused by drug withdrawal. The users then crave the drug during other kinds of distress.

Stop & Check

5. Someone who is quitting an addictive substance for the first time is strongly counseled not to try it again. Why?

See page 468 for the answer.

Predispositions

Most people drink alcohol in moderation, but others develop a habit of abuse. With other substances also, only some of the users develop an addiction. Evidently people differ in their predisposition to substance abuse. Even among mice, some develop compulsive alcohol use when given the opportunity, and some do not (Siciliano et al., 2019).

A great deal of the predisposition depends on experience. People who had abusive experiences in childhood are more vulnerable, as is a child whose mother drank too much alcohol during pregnancy (Baer et al., 2003; Cornelius et al., 2016). Children who grew up without careful parental supervision are more likely to develop impulse problems than children of more attentive parents (Dick et al., 2009).

Adult environment is especially important for late-onset alcoholism. As a rule, people with early-onset alcoholism (before age 25) have a family history of alcoholism, a genetic predisposition, and a rapid onset of the problem. People with later onset are more likely to have reacted to life difficulties, less likely to have a family history of alcoholism, and more likely to respond well to treatment (Brown et al., 1994).

Genetic Influences

The probability of abusing alcohol or other drugs also relates to genetic influences. Parents' alcohol use correlates more strongly with that of their biological children than their adopted children (McGue et al., 2014). Several genes affect the probability of substance use, with effects that vary from one environment to another (Guillot et al., 2015). Most of these genes are non-specific, increasing the risk of several mental disorders, and risk-taking behaviors in general (Linnér et al., 2021; Pasman et al., 2018; Walters et al., 2018).

One gene with a well-confirmed influence on alcohol abuse controls the metabolism of alcohol. In fact, this is the only case of a common gene with a substantial effect on a human psychological disorder (other than Huntington's disease). After anyone drinks ethyl alcohol, enzymes in the liver metabolize it to *acetaldehyde,* a toxic substance. The enzyme *acetaldehyde dehydrogenase* then converts acetaldehyde to *acetic acid,* a chemical that the body uses for energy:

$$\text{Ethyl alcohol} \longrightarrow \text{Acetaldehyde} \xrightarrow[]{\substack{\text{Acetaldehyde}\\ \text{dehydrogenase}}} \text{Acetic acid}$$

People with a gene that produces less acetaldehyde dehydrogenase metabolize acetaldehyde more slowly. If they drink much alcohol, they accumulate acetaldehyde, which produces flushing of the face, increased heart rate, nausea, headache, abdominal pain, impaired breathing, and tissue damage. Acetaldehyde is probably responsible for hangovers, although research on hangovers is sparse. More than a third of the people in China and Japan have a gene that slows acetaldehyde metabolism. Probably for that reason, alcohol abuse has historically been uncommon in those countries (Luczak et al., 2006; Samochowiec et al., 2014) (Figure 14.3).

Figure 14.3 Robin Kalat (the author's daughter) finds an alcohol vending machine on a sidewalk in Tokyo in 1998

Restrictions against buying alcohol were traditionally weak in a country where many people cannot quickly metabolize acetaldehyde and therefore drink alcohol in moderation. In 2000, Japan banned alcohol vending machines in public places.

KIRIN BEER
キリンビール

James W. Kalat

Behavioral Predictors of Abuse

If genes, early environment, or anything else predisposes certain people to drug or alcohol abuse, presumably the predisposition alters behavioral reactions to the substance. If so, it should be possible to monitor behavior of young people and predict their risk for later problems. Doing so might be useful. By the time someone has developed a serious substance abuse problem, overcoming it is difficult. If we could identify people at risk before they develop a significant problem, could intervention be more successful? It is worth a try.

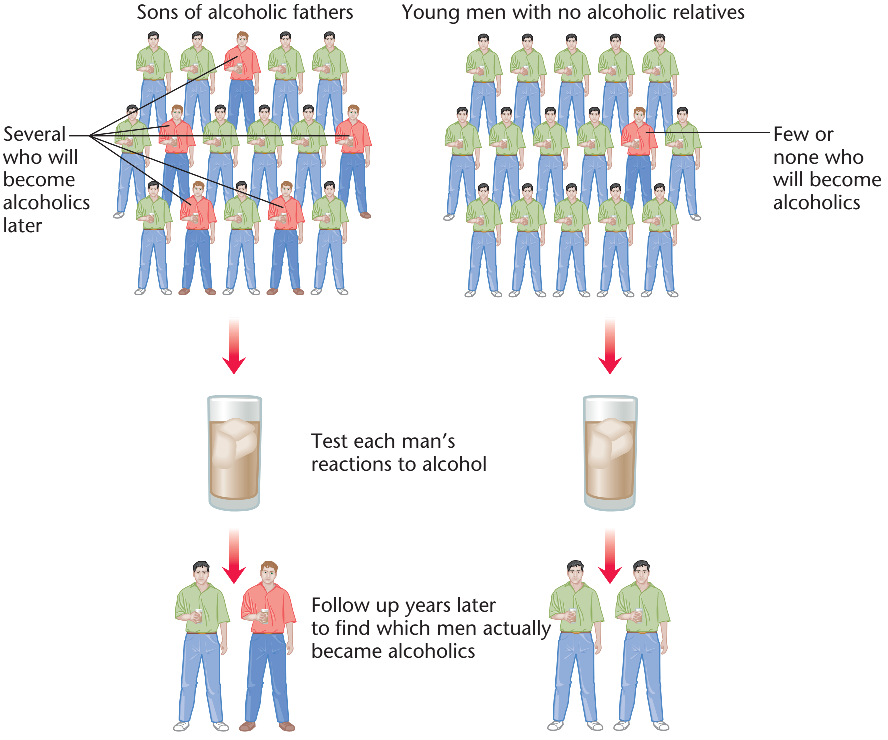
To identify people at risk, one strategy is to study huge numbers of people for years: Measure as many factors as possible for a group of children or adolescents, later determine which of them developed alcohol problems, and then see which early factors predicted the onset of alcoholism. Such studies find that alcoholism is more likely among those who were described in childhood as impulsive, risk taking, easily bored, sensation seeking, and outgoing (Dick et al., 2000; Legrand et al., 2005).

Other research follows this design: First, identify young men who are not yet problem drinkers. (Researchers focused first on men, because early-onset alcoholism is more common in men.) Compare men whose fathers had alcoholism to men who have no close relative with an alcohol problem. Because of the strong familial tendency toward alcoholism, researchers expect that many of the sons of alcoholics are future alcoholics themselves. The idea is that any behavior more common in the sons of alcoholics is probably a predictor of future alcoholism (Figure 14.4).

The most robust finding is that most sons of alcoholics show less than average intoxication after drinking a moderate amount of alcohol. They report feeling less drunk and show less body sway (Schuckit and Smith, 1996). Presumably, someone who starts feeling tipsy after a couple of drinks stops at that point. People who “hold their liquor well” continue drinking, perhaps enough to impair their judgment. Follow-up studies found that men who report low intoxication after moderate drinking are more likely than others to develop an alcohol abuse problem (Schuckit and Smith, 1997; Schuckit and Smith, 2013). Similar results have been reported for women (Eng et al., 2005). If someone with strong intoxication from a moderate intake does develop an alcohol problem, it is usually less severe than that of other abusers (Schuckit et al., 2018). The advice is, if you “hold your liquor well,” it is not something to brag about, but something to worry about.

Figure 14.4 Design for studies of predisposition to alcoholism

Sons of alcoholic fathers are compared to other young men of the same age and same current drinking habits. Any behavior that is more common in the first group is presumably a predictor of later alcoholism.


Sons of alcoholic fathers
Young men with no alcoholic relatives
Several who will become alcoholics later
Few or none who will become alcoholics
Test each man’s reactions to alcohol
Follow up years later to find which men actually became alcoholics

(**Source:** © Cengage Learning 2013)

Stop & Check

6. How does predisposition to alcohol abuse relate to how the liver metabolizes alcohol?
7. What behavior is positively correlated with an increased probability of later developing alcohol abuse?

See page 468–469 for the answer.

Treatments

Research has revealed much about the mechanisms of addiction. Unfortunately, our increased understanding has not yet translated into better forms of treatment (Venniro et al., 2020). In fact, that is the case for psychopathology in general. Research over recent decades has learned much about the genes, neurotransmitters, and other biological

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factors related to disorders, but treatment outcomes have not improved noticeably (Insel, 2022). The most common treatment for substance abuse, especially in the United States, is participation in Alcoholics Anonymous, Narcotics Anonymous, or similar organizations. A smaller number of people consult a psychotherapist. Not many people turn to medications, but a few options are available.

Medications to Combat Alcohol Abuse

As mentioned, the liver metabolizes alcohol into acetaldehyde (toxic) and then into acetic acid (harmless). The drug *disulfiram,* which goes by the trade name **Antabuse,** antagonizes the enzyme that metabolizes acetaldehyde. Consequently, anyone who takes Antabuse becomes ill after drinking alcohol. The effects of Antabuse were discovered by accident. The workers in one rubber-manufacturing plant found that when they had disulfiram on their skin, they developed a rash (Schwartz and Tulipan, 1933). If they inhaled disulfiram, they couldn't drink alcohol without getting sick. Soon therapists tried using disulfiram as a drug, hoping that those with alcoholism would associate alcohol with illness and stop drinking.

Most studies find that Antabuse is about equal to a placebo. Ordinarily, that result would indicate that a drug is ineffective, but Antabuse is a special case because of *why* it is similar to the placebo. When people take Antabuse, or a placebo that they think might be Antabuse, the threat of becoming ill strongly discourages any attempt to drink alcohol. As long as they do not try alcohol, of course, they do not know whether they were actually taking Antabuse. Antabuse is about equal to placebo not because Antabuse is ineffective, but because thinking that a placebo might be Antabuse makes the placebo effective (Fuller and Roth, 1979; Skinner et al., 2014). In either case, taking the daily pill reaffirms a pledge to avoid alcohol. Someone who takes an Antabuse pill and then drinks alcohol anyway becomes ill, and probably quits taking Antabuse instead of alcohol.

A related idea is to have people drink alcohol and then immediately take a drug that produces nausea, thereby forming a learned aversion to the taste of the alcohol. That procedure usually produces quick and effective avoidance of alcohol, although its use has never been popular (Revusky, 2009).

Other medications are naloxone (trade name Revia) and naltrexone, which block opiate receptors and thereby decrease the pleasure from alcohol. Acamprosate is about equal to naltrexone in effectiveness, although its mechanism of effect remains uncertain (Jonas et al., 2014).

Medications to Combat Opiate Abuse

Heroin is an artificial substance invented in the 1800s as a supposedly safer alternative for people who were trying to quit morphine. Some physicians at the time recommended that people using alcohol switch to heroin (Siegel, 1987). They abandoned this idea when they discovered the addictiveness of heroin.

Still, the idea has persisted that people who cannot quit opiates might switch to a less harmful drug. **Methadone** (METH-uh-don), similar to heroin and morphine, activates the same brain receptors and produces the same effects, but it has the advantage that it can be taken orally. Methadone taken orally slowly enters the blood and then the brain, avoiding a "rush" that disrupts behavior. Because methadone leaves the brain slowly, the withdrawal symptoms are also gradual. Furthermore, users avoid the risk of an injection with a possibly infected needle. However, methadone does not eliminate the addiction. If someone quits using methadone, the cravings return.

Buprenorphine and levomethadyl acetate (LAAM), drugs similar to methadone, are also used to treat opiate addiction. LAAM has the advantage of producing a long-lasting effect so that the person visits a clinic three times a week instead of daily. People using any of these drugs live longer and healthier, on average, than heroin or morphine users, and they are far more likely to hold a job (Vocci et al., 2005). However, the drugs do not end the addiction. They merely satisfy the craving in a less dangerous way.

Anecdotal reports have stated that a drug called ibogaine reduces cravings and decreases the probability of drug relapse. However, ibogaine causes hallucinations, and it can damage the heart. Researchers developed a related drug that is both safer and easier to synthesize. So far, we know that it reduces alcohol and heroin seeking in mice, and we await results from human trials (Cameron et al., 2021).

Stop & Check

8. How does Antabuse work?
9. Methadone users who try taking heroin experience little effect from it. Why?

See page 469 for the answer.

Module 14.1 | In Closing

The Psychology and Biology of Substance Abuse

Many people say that alcoholism or other drug addiction is a disease. Is it? The medical profession has no firm definition of *disease*. Dis-ease is literally lack of ease, so in a sense anything that causes difficulty in life is a disease. Calling addiction a disease helps to reduce some of the guilt and stigma. However, the term *disease* is generally taken to imply that the problem calls for medical intervention.

As you have seen in this module, addiction does have a physiological basis. Many genes increase the risk of addiction. Addiction alters the brain's reaction to the drug, cues for the drug, and other events. However, addiction also reflects a history of experiences. Although medical treatments can help, behavioral interventions are still the most common treatments. Addiction is a complex problem that requires attention to both the physiology and the social environment.

Summary

1. The effects of a drug vary because people differ in their abundance of several types of receptors. **463**
2. Addictive drugs and many other reinforcing experiences release dopamine in the nucleus accumbens. Dopamine may be more important for the motivation (wanting) than for pleasure. **463**
3. The cravings associated with an addiction represent "wanting" more than "liking." **464**
4. After someone becomes addicted to a substance, the substance releases less dopamine in the nucleus accumbens, but cues associated with it release more. **464**
5. Cues associated with an addictive substance continue to grab attention and trigger a craving even after a period of abstinence. **464**
6. Repeated use of a drug leads to tolerance and the potential for withdrawal symptoms. **464**
7. Someone who uses a drug during withdrawal symptoms may learn to use it to overcome stress of other types. **465**
8. Predispositions to alcohol or drug abuse arise from both environment and genetics. Early-onset alcoholism reflects a stronger genetic predisposition than does later-onset alcoholism. **465**
9. People who drink alcohol with relatively little sign of intoxication are more likely than other people to develop alcohol abuse. **466**
10. Several drugs including Antabuse and methadone help some people decrease their use of alcohol or opiates. **467**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

affinity **463**
agonist **463**
Antabuse **467**
antagonist **463**
craving **464**
efficacy **463**
methadone **467**
nucleus accumbens **463**
self-stimulation of the brain **463**
tolerance **464**
withdrawal **464**

Thought Question

The research on sensitization of the nucleus accumbens dealt with addictive drugs, mainly cocaine. Would you expect a gambling addiction to have similar effects? How could someone test this possibility?

Stop & Check Answers

1. It is an antagonist because, by occupying the receptor, it blocks out the neurotransmitter.
2. They increase the release of dopamine in the nucleus accumbens.
3. The nucleus accumbens becomes less responsive to the drug, but more sensitive to cues associated with the drug. Although a given dose of the drug produces less pleasure than before, cues trigger a craving for it.
4. Even after a period of abstention, a cue for the drug grabs attention and triggers a craving. Also, the decreased activity in the prefrontal cortex means less ability to inhibit an impulse.
5. Taking an addictive drug during the withdrawal period is likely to lead to a habit of using the drug to relieve other kinds of distress.
6. The liver metabolizes alcohol to acetaldehyde, which is toxic, and then to acetic acid. People whose enzymes are slow to metabolize acetaldehyde to acetic acid are

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less likely than others to abuse alcohol, because rapid or excessive drinking makes them ill.

7. People who show less intoxication, including less body sway, after drinking a moderate amount of alcohol are more likely than average to develop alcohol abuse.
8. Antabuse blocks the enzyme that converts acetaldehyde to acetic acid. It therefore makes people sick if they drink alcohol. Its effectiveness depends on the fact that someone knows or believes that drinking alcohol will cause illness.
9. Because methadone is already occupying the endorphin receptors, heroin cannot add much stimulation to them.

Module 14.1 | End-of-Module Quiz

1. Which of the following drugs would be a strong agonist?
- **a.** One with high affinity and high efficacy
- **b.** One with high affinity and low efficacy
- **c.** One with low affinity and high efficacy
- **d.** One with low affinity and low efficacy

2. The rewarding effects of a potentially addictive substance depend on the release of dopamine in which brain area?
- **a.** Nucleus accumbens
- **b.** Fusiform gyrus
- **c.** Lateral hypothalamus
- **d.** Cingulate gyrus

3. How does dopamine release change after someone develops an addiction?
- **a.** Increased response to drug cues, but decreased response to the drug itself
- **b.** Decreased response to drug cues, but increased response to the drug itself
- **c.** Increased response to both drug cues and the drug itself
- **d.** Decreased response to both drug cues and the drug itself

4. The cues associated with an addictive substance are largely responsible for which of the following?
- **a.** Pleasure
- **b.** Tolerance
- **c.** Cravings
- **d.** Withdrawal symptoms

5. Drug tolerance is greater if the drug is taken in the usual location than if it is taken elsewhere. What conclusion does this observation imply?
- **a.** Tolerance depends on changes in the release of dopamine.
- **b.** Tolerance depends on learning.
- **c.** Tolerance depends on the metabolic breakdown of the drug.
- **d.** Tolerance depends on the release of hormones.

6. Which type of alcohol abuse is most strongly associated with a genetic predisposition?
- **a.** Late onset
- **b.** Early onset
- **c.** Female
- **d.** Mild

7. One gene is known to exert a strong effect on the probability of alcohol abuse. How does that gene exert its effects?
- **a.** By altering the taste and aftertaste of alcoholic beverages
- **b.** By influencing how strongly the prefrontal cortex inhibits impulses
- **c.** By controlling how the liver metabolizes alcohol
- **d.** By changing the release of steroid hormones

8. Which of the following is correlated with an increased probability of developing alcohol abuse?
- **a.** Being left-handed
- **b.** Low amounts of the enzyme that converts acetaldehyde to acetic acid
- **c.** Less than average intoxication after moderate alcohol intake
- **d.** Growing up in a family of non-drinkers

9. Why do placebos generally produce about the same effects as Antabuse?
- **a.** Antabuse has no physiological effects.
- **b.** Placebos satisfy the craving for alcohol.
- **c.** People who think they are taking Antabuse avoid drinking.
- **d.** Placebos tend to relieve pain.

10. What is the advantage of taking methadone instead of morphine or heroin?
- **a.** Methadone is not addictive.
- **b.** Someone can gradually taper off methadone and become drug-free.
- **c.** Methadone is readily available without a prescription.
- **d.** Methadone satisfies the craving without seriously disrupting behavior.

Answers: 1a, 2a, 3a, 4c, 5b, 6b, 7c, 8c, 9c, 10d.

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Module 14.2

Mood Disorders

Learning Objectives

After studying this module, you should be able to:

6. Describe the symptoms and characteristics of major depression.
7. Discuss the genetic and environmental predispositions toward depression.
8. Describe and evaluate the standard antidepressant drugs and the available alternatives.
9. Describe bipolar disorder and its treatment.

Depression is a common, often-debilitating disorder. Surveys usually report that about 5 to 6 percent of adults in the United States and Canada have a clinically significant depression within a given year, and 10 to 20 percent do at some point in life (Narrow et al., 2002; Kessler et al., 2005). Events modify these numbers. During 2020, at the peak of the COVID-19 epidemic and a period of social unrest, prevalence of depression in the United States rose to 24 percent (Twenge et al., 2021). Even after people recovered from COVID, they had an increased risk of depression, anxiety, substance abuse, and cognitive decline (Al-Aly, 2022).

Depression is more common in women than men, from the onset of puberty through menopause, although the prevalence is about equal before or after that period (Mendle et al., 2016). For many years, laboratory research on the biological basis of depression used only male rodents, based on the assumption that females are more variable (and therefore that using just males could get reliable results with fewer animals), and on the assumption that the mechanisms of emotional reactions are probably the same for males and females. The assumption about greater variability is probably wrong, and the assumption about identical mechanisms is definitely wrong. Stimulating oxytocin neurons in the prefrontal cortex elicits anxiety in male mice but it elicits prosocial behavior in females. Stimulating cannabinoid receptors elicits freezing in males and darting in females. Receptors for corticotropin releasing factor are more sensitive in females than in males, producing hyperarousal under certain conditions. Researchers have sometimes developed an antidepressant treatment based on research using male rodents, and then wondered why it was so ineffective when they tested it on a human population of mostly women (Bangasser and Cuarenta, 2021).

Major Depressive Disorder

Everyone has times of feeling discouraged. Major depression is prolonged and more intense. People with **major depression** feel sad and helpless most of the day every day for weeks at a time (Figure 14.5). Measurements from the nucleus accumbens show less response to reward (Russo and Nestler, 2013). Other common symptoms include attention problems, low motivation, and impaired memory. The cognitive limitations often persist even after successful treatment of the mood problems (Gonda et al., 2015).

Absence of happiness is an important symptom. In one study, people carried a beeper that sounded at unpredictable times to signal them to describe their emotional reactions. People with depression reported only

Figure 14.5 Depression as a visible condition

People with depression display their condition through facial expression, posture, and tone of voice.

TZIDO SUN/Shutterstock.com

an average number of unpleasant experiences but far below the average number of pleasant ones (Peeters et al., 2003). In other studies, people examined photographs or films as researchers recorded their reactions. People with depression reacted normally to sad or frightening depictions but seldom smiled at the comedies or pleasant pictures (Rottenberg et al., 2002; Sloan et al., 2001). In addition to the lack of pleasure, depression is marked by "negative bias," a tendency to interpret events in a discouraging way.

Almost everyone with depression has sleep problems, which generally precede the mood changes (Li et al., 2016). The usual sleep pattern for people with depression resembles the sleep of healthy people after traveling a couple of time zones west: They fall asleep when the clock says to do so, but they enter REM sleep sooner than average, and they awaken early, as Figure 14.6 illustrates.

In most cases, people have episodes of depression separated by periods of normal mood. Several studies reported that the early episodes were longer, and that later episodes were briefer but more frequent (e.g., Post, 1992). A later analysis showed that these reports reflected a statistical artifact: Suppose you measure the mean length of all first episodes. That will include anyone who ever became depressed, including some who had just one episode lasting many years. When you measure the mean length of all fifth episodes or all tenth episodes, you study only people who had at least five or ten episodes. To have that many episodes, each of them had to be brief. If you compare the length of, say, first and fifth episodes but include only people who had at least five episodes, the mean lengths are about the same (Anderson et al., 2016).

Genetics

Studies of twins and adopted children indicate a moderate degree of heritability for depression (Shih et al., 2004). As with substance abuse, heritability is higher for early-onset depression than for depression later in life (Wium-Andersen et al., 2020). Researchers have identified at least 17 common genetic variants linked to depression (Levey et al., 2021), each with small effects. The results differ among populations. A study of Chinese women with recurrent severe depression identified two genes with a strong effect. Those genes did not emerge in studies on Europeans, simply because those genes are rare in Europe (CONVERGE Consortium, 2015).

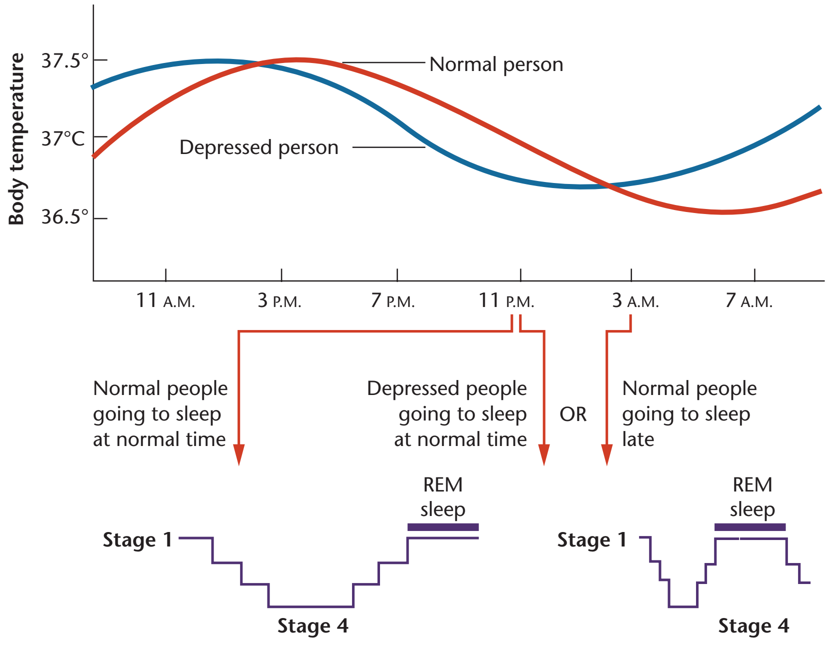
One research problem is that when we talk about depression, we are probably combining two or more syndromes. People with early-onset depression (before age 30) have a high probability of having other relatives with psychiatric problems, not always depression (Fu et al., 2002; Gade et al., 2014; Hudson et al., 2003). People with late-onset depression (especially after age 45 to 50) have a high probability of relatives with circulatory problems (Kendler et al., 2009). Researchers identified four genetic variants linked specifically to early-onset depression (Kang et al., 2021).

An influential study reported that one genetic variant related to serotonin reuptake increased the risk of depression only for people with a history of major stressful experiences (Caspi et al., 2003). That is, the gene did not necessarily lead to depression, but it magnified the reaction to stressful events. This was an exciting idea, but later results were inconsistent, and the largest attempt to replicate it found no support for the hypothesis (Border et al., 2019).

Are genes that can produce depression just a mistake, or might we have them for a reason? Evolutionary psychologists have proposed the hypothesis that depression could be an adaptation to conserve energy after a defeat. Perhaps depression served a purpose for our ancestors after physical injuries, even if it is less adaptive today after more symbolic types of setbacks (Beck and Bredemeier, 2016).

Figure 14.6 Circadian rhythms and depression

Most people with depression have their circadian rhythms advanced by several hours.



(**Source:** Bottom graphs from *Sleep,* by J. Allan Hobson, ©1989, 1995 by J. Allan Hobson. Reprinted by permission of Henry Holt and Company, LLC.)

Stop & Check

10. On average, how does the sleep pattern differ from average when people are depressed?
11. Why is it important to analyze genetic results separately for different ethnic groups?
12. What evidence suggests that two types of depression are influenced by different genes?

See page 479 for the answer.

Pain and Stress

Although a genetic predisposition can make depression more likely, events in the environment are the immediate triggers. Pain is so closely associated with depression that some languages use the same word for both. Pain decreases the activity of dopamine neurons that are important for both motivation and reward (Markovic et al., 2021).

Many kinds of stress can cause depression. Depression often occurs in women shortly after giving birth, or around the time of menopause, events that put much strain on the body. Most of the women who experience depression at those times had previous bouts of depression, and the stress of delivery or menopause triggered a recurrence (Maki et al., 2019).

Stressful events activate the immune system, preparing the body to attack an infection. The immune system releases proteins called cytokines that fight an infection and conserve energy by reducing activity levels and decreasing appetite (Hodes et al., 2015; Kaplan et al., 2015; Wohleb et al., 2016). Inactivity and loss of appetite are typical symptoms of depression.

Many of the cytokines released by the immune system produce inflammation, and many people with depression show signs of brain inflammation (Woelfer et al., 2019). Inflammation impairs the activity of mitochondria, resulting in decreased energy, another symptom of depression (Kramer and Bressan, 2018).

Antidepressant Drugs

One insight into possible biological bases of depression comes from research on drugs that relieve it. You might assume that investigators first determine the causes of a psychological disorder and then develop medications based on the causes. The opposite has been more common: Investigators find drugs that seem helpful, and then they try to understand how the drugs work. Iproniazid, the first antidepressant drug, was originally marketed to treat tuberculosis, until physicians noticed that it relieved depression. Chlorpromazine was originally used as a tranquilizer, until physicians noticed its ability to alleviate schizophrenia. For decades, researchers evaluated drugs just by trial and error. Today, researchers start by testing drugs in test tubes or tissue samples, in order to use fewer laboratory animals.

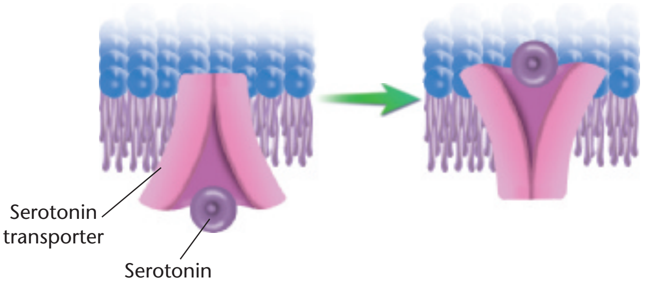
Standard Antidepressants

Antidepressant drugs include tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants. The **tricyclics** (e.g., imipramine, trade name Tofranil) operate by blocking the transporter proteins that reabsorb serotonin, dopamine, and norepinephrine into the presynaptic neuron after their release. Figure 14.7 shows how the serotonin transporter protein picks up a serotonin molecule outside the membrane and then flips to deliver the molecule inside the neuron. A tricyclic drug locks the transporter into its initial position and blocks reuptake, thus prolonging the presence of the neurotransmitters in the synaptic cleft (Penmatsa et al., 2013; H. Wang et al., 2013). Tricyclics also block histamine receptors, acetylcholine receptors, and certain sodium channels (Horst and Preskorn, 1998). Blocking histamine produces drowsiness, blocking acetylcholine leads to dry mouth and difficulty urinating, and blocking sodium channels causes heart irregularities. People need to limit their use of tricyclic drugs to minimize these side effects.

Selective serotonin reuptake inhibitors (SSRIs) attach to the center of just the serotonin transporter protein and lock it into a shape that blocks serotonin from binding to it (Coleman et al., 2016). SSRIs produce milder side effects than the tricyclics, but their effectiveness is about the same. Common SSRIs include fluoxetine (trade name Prozac), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), and paroxetine (Paxil or Seroxat). As you might guess, **serotonin norepinephrine reuptake inhibitors (SNRIs)**, such as duloxetine (Cymbalta) and venlafaxine (Effexor), block reuptake of both serotonin and norepinephrine. Perhaps surprisingly, antidepressants that target different neurotransmitters are about equally effective (Montgomery et al., 2007; Undurraga and Baldessarini, 2012). Given the variety of symptoms associated with depression, it seems reasonable to try a combination of antidepressant drugs instead of

Figure 14.7 Reuptake of serotonin into the presynaptic neuron

The serotonin transporter protein is open to the outside of the neuron on the left. After it picks up a serotonin molecule, it flips position to deliver the serotonin to the inside of the presynaptic neuron. Tricyclic and SSRI antidepressants lock the transporter protein into the position shown at the left, preventing reuptake.



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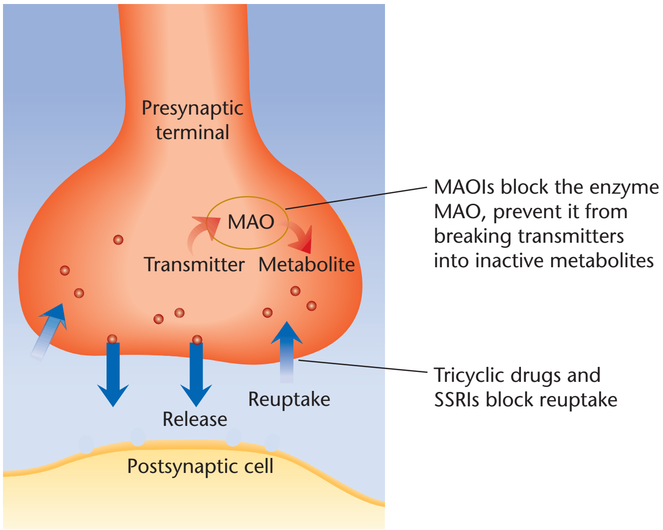
just one, and many psychiatrists do so, routinely. However, researchers have reported that a combination of drugs increases the number of side effects without demonstrably improving the antidepressant response (Stassen et al., 2021).

The **monoamine oxidase inhibitors (MAOIs)** (e.g., phenelzine, trade name Nardil) block monoamine oxidase (MAO), a presynaptic enzyme that breaks catecholamines and serotonin into inactive forms. When MAOIs block this enzyme, the presynaptic terminal has more of its transmitter available for release. The MAOIs were the earliest antidepressants, but today physicians prescribe them only for patients who did not respond to other antidepressants. People taking MAOIs must avoid foods containing tyramine—including cheese, raisins, and many others—because a combination of tyramine and MAOIs increases blood pressure. The **atypical antidepressants** are a miscellaneous category (Horst and Preskorn, 1998). One example is bupropion (Wellbutrin), which inhibits the reuptake of dopamine and to some extent norepinephrine. Figure 14.8 summarizes the mechanisms of tricyclics, SSRIs, and MAOIs.

Many people use St. John's wort, an herb, as an antidepressant. Because it is a nutritional supplement instead of a drug, the U.S. Food and Drug Administration does not regulate it, and its purity varies from one bottle to another. It has the advantage of being less expensive than antidepressant drugs. An advantage or disadvantage, depending on your point of view, is that it is available without prescription. People can get it easily but often take inappropriate amounts. Its effectiveness is reportedly comparable to that of standard antidepressant drugs (Sarris et al., 2011), but it has a worrisome side effect: St. John's wort increases the effectiveness of a liver enzyme that breaks down plant toxins, and also breaks down most medicines. Therefore, taking St. John's wort decreases the effectiveness of other drugs you might be taking—antidepressant drugs, cancer drugs, AIDS drugs, and others (He et al., 2010; Moore et al., 2000).

Figure 14.8 Routes of action of antidepressants

Tricyclics block the reuptake of dopamine, norepinephrine, and serotonin. SSRIs specifically block the reuptake of serotonin. SNRIs block reuptake of serotonin and norepinephrine. MAOIs block the enzyme MAO, which converts dopamine, norepinephrine, or serotonin into inactive chemicals.


Presynaptic terminal
MAO
Transmitter
Metabolite
Release
Reuptake
Postsynaptic cell
MAOIs block the enzyme MAO, prevent it from breaking transmitters into inactive metabolites
Tricyclic drugs and SSRIs block reuptake

(**Source:** © Cengage Learning 2013)

Stop & Check

13. What are the effects of tricyclic drugs?
14. What are the effects of SSRIs?
15. What are the effects of MAOIs?

See page 479 for the answer.

How Do Antidepressants Act?

When researchers discovered antidepressants that increase the availability of serotonin and other neurotransmitters, they at first assumed that the cause of depression was a deficiency of serotonin or other neurotransmitters. The explanation cannot be that simple. Procedures that suddenly decrease serotonin levels do not provoke feelings of depression in most people (Neumeister et al., 2004, 2006). Most importantly, the time course does not fit: Antidepressants reach the brain within minutes to hours, but people generally need to take the drugs for at least 2 weeks before they experience noticeable benefits (Stewart et al., 1998).

Besides increasing levels of serotonin and other transmitters, another action these drugs have in common is to facilitate neurotrophins. Depression is associated with decreased levels of the neurotrophin called *brain-derived neurotrophic factor* (BDNF), which is important for synaptic plasticity and learning (Martinowich et al., 2007; Sen et al., 2008). As a result of low BDNF, depression is associated with impaired learning. Standard antidepressants attach to a receptor for BDNF and facilitate its release. However, because they do not bind strongly to that receptor, they have to accumulate for weeks to reach a high enough brain concentration to produce a significant effect (Casarotto et al., 2021). This result fits with the known time course for the drugs. A mutation in the receptor for BDNF prevents antidepressants from exerting their effects (Airan et al., 2007).

Stop & Check

16. What is one explanation for why standard antidepressants produce benefits so slowly?
17. How might we explain why the drugs generally do not improve mood for people not suffering from depression?

See page 479 for the answer.

How Effective Are Antidepressants?

So far, we have considered explanations of how antidepressants work. How sure are we that they *do* work? Not everyone is convinced (Kirsch, 2010, 2019), and we must at least say that their effectiveness is limited.

Most controlled studies find that antidepressants are at least moderately more effective than placebos, but even when the advantage over placebos is statistically significant, it is not always strong in a clinical sense (Bschor and Kilarski, 2016; Undurraga and Baldessarini, 2012). Figure 14.9 summarizes the results of many experiments in which people were randomly assigned to antidepressant drugs or placebos. The horizontal axis represents scores on the Hamilton Depression Rating Scale at the start of treatment, where higher scores indicate more intense depression. The vertical axis represents amount of improvement. Triangles represent patients receiving the drug in a study, and circles represent patients receiving a placebo. The size of the triangle or circle is proportional to the number of patients in a group. Many people respond well on placebos, either because of spontaneous recovery over time or because of the expectation that comes from taking a pill. When people take an antidepressant drug and gradually improve, both they and their psychiatrists are likely to attribute the improvement to the pills, even when the improvement may have been a placebo effect.

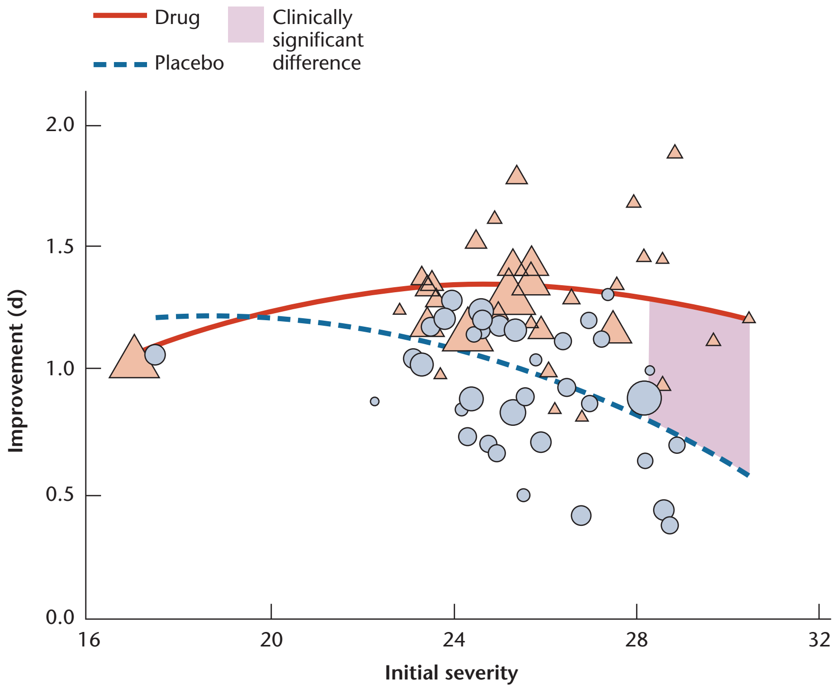
For patients with mild to moderate depression, the differences between the drug group and the placebo group appear too small to be meaningful (Kirsch et al., 2008). However, these data probably understate the effectiveness of the drugs at lower levels of depression, where the Hamilton Depression Rating Scale has lower reliability and validity (Fountoulakis et al., 2013; Isaacson and Adler, 2012). In fact, it is an imperfect measure for any level of depression. Nevertheless, the point remains that antidepressant drugs have limited and variable effectiveness.

When people take antidepressants, many fail to show a benefit from the first drug they try. After a few weeks, the psychiatrist might prescribe a different drug, and then perhaps another one, and so forth, on a trial-and-error process. Most patients eventually show a favorable response, regardless of whether they switch to a similar drug or a drug of a different type (Keers and Uher, 2012). However, how can we be sure that switching drugs was responsible for the improved mood? When someone goes through a series of drugs, we don't know whether the patient would have recovered over that much time on the first drug, or perhaps without any drug at all. Many research studies have failed to include adequate control groups.

Psychiatrists also sometimes increase the dose. Again, the problem is, if someone begins to respond to a higher dose, we don't know whether the improvement was due to the higher dose or just to the passage of time. Controlled studies find little evidence that different doses of SSRIs produce different effects (Braun et al., 2020).

Figure 14.9 Mean improvement from depression by people taking antidepressants or placebos

Pink triangles represent people taking medications in a particular study. Gray circles represent people taking placebos. The size of the triangle or circle is proportional to the number of people in the study. The ordinate shows d, which is a measure of effect size.



(**Source:** From Kirsch et al., 2008.)

Psychedelics as Medications

Can we do better than standard antidepressants? In the 1950s and 1960s, several psychotherapists reported successful results from using **psychedelics** to aid treatments—that is, drugs that distort perception. The scientific quality of the early research was weak, and the drugs developed a bad reputation for several reasons. Decades later, research resumed, finding that LSD or psilocybin can help relieve depression, anxiety, PTSD, and substance abuse. In addition to effects on serotonin synapses, these drugs enhance neural plasticity (Shao et al., 2021), helping people replace rigid, harmful thought patterns. They also tend to enhance social functioning. The research is still not scientifically strong, partly because

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of the difficulty of doing a placebo-controlled study. (People know whether they took the drug or the placebo because a placebo produces no psychedelic effects.) Still, the benefits appear to be real in many cases, developing faster than those of other drugs and lasting for weeks or months. MDMA (3,4-methylenedioxy-methamphetamine, or "ecstasy") also helps some people overcome depression, while acting through different chemical pathways.

Unlike the standard antidepressant drugs, the psychedelics must be administered in a therapeutic session with careful supervision, to avoid serious risks. A typical protocol is a 4- to 5-hour session of relaxation under the psychedelic influence, followed by a discussion with a therapist the next day, and then a second session later (Davis et al., 2021; Nutt and Carhart-Harris, 2021). This is hardly an inexpensive treatment, and as with any other antidepressant treatment, it is not effective for everyone.

Ketamine is another hallucinogenic drug that can decrease depression rapidly, with benefits that last for weeks. Two mechanisms account for its benefits: First, it facilitates the BDNF receptor, increasing synaptic plasticity. It attaches more strongly than standard antidepressant drugs do, accounting for its more rapid effects (Aguilar-Valles et al., 2021; Casarotto et al., 2021). Second, ketamine blocks NMDA-type receptors in an area called the lateral habenula, which responds to unpleasant experiences (Yang et al., 2018). Unfortunately, it also attaches to receptors that produce hallucinations and delusions. Although it does not have a high risk of addiction, it is sufficiently disorienting that the treatment requires careful supervision (Simmler et al., 2022). Someone who has just used ketamine could not safely drive home, for example. It also activates AMPA-type glutamate receptors.

Like psilocybin and LSD, the Food and Drug Administration has never approved ketamine for treating psychiatric disorders, although it permits experimental research. Nevertheless, long ago it did approve ketamine for use as an anesthetic, and when a drug is approved for one purpose, nothing stops a physician from prescribing it for other purposes. Ketamine is, therefore, increasingly used for treating depression (De Gregorio et al., 2021). The FDA did approve one isomeric form of ketamine, esketamine or Spravato®, as a nasal spray treatment for adults with treatment-resistant depression. A large dose of either ketamine or esketamine has the risk of inducing an episode of schizophrenia, and even a small dose can induce those symptoms in someone with a genetic predisposition (Uno and Coyle, 2019). Researchers discovered that the psychedelic drugs exert their effects by stimulating several sites on serotonin type 2A receptors. Evidently, the hallucinogenic effects depend mostly on one site and the antidepressant effects depend mostly on another site, and therefore it may be possible to develop new drugs with the benefits of the psychedelics, but with less risk (Cao et al., 2022).

Alternatives to Medication

Cognitive behavioral therapy and other forms of psychotherapy produce benefits that are about equal to the effects of antidepressant drugs (Zhang et al., 2019). Brain scans show that psychotherapy and antidepressants increase metabolism in the same brain areas (Brody et al., 2001; S. D. Martin et al., 2001). That similarity should not be surprising. If mental activity is the same thing as brain activity, then changing thoughts and changing brain chemistry are the same thing.

Psychotherapy has two advantages. One is the lack of side effects, and the other is that its effects are more likely to last. Most people relapse into depression sooner after antidepressant drug treatment than after psychotherapy (Steinert et al., 2014). The disadvantage of psychotherapy is convenience. It is easier to take a pill than to visit the therapist's office.

Would a combination of antidepressant drugs and psychotherapy work better than either one alone? On average, people receiving both treatments show more rapid improvement than people receiving either one alone, but the percentage of people showing improvement increases only slightly (de Maat et al., 2008; Hollon et al., 2014). Evidently, not many people respond to one treatment and not the other.

Stop & Check

18. As depression becomes more severe, what happens to the percentage of patients showing improvement while taking antidepressant drugs or placebos?
19. What is an advantage of psychotherapy over antidepressant drugs?

See page 479 for the answer.

Electroconvulsive Therapy and Brain Stimulation

Another option, despite its stormy history, is treatment through an electrically induced seizure, known as **electroconvulsive therapy (ECT)**. ECT originated with the observation that if someone had both epilepsy and schizophrenia, when symptoms of one disorder increase, symptoms of the other often decrease (Trimble and Thompson, 1986). In the 1930s, Ladislas Meduna and other physicians tried to relieve schizophrenia by inducing convulsions with a large dose of insulin. Insulin shock is a dreadful experience, however, and difficult to control. An Italian physician, Ugo Cerletti, after experimenting with animals, developed a method of inducing seizures with an electric shock through the head (Cerletti and Bini, 1938). Electroconvulsive therapy is quick, and most patients awaken calmly without remembering it.

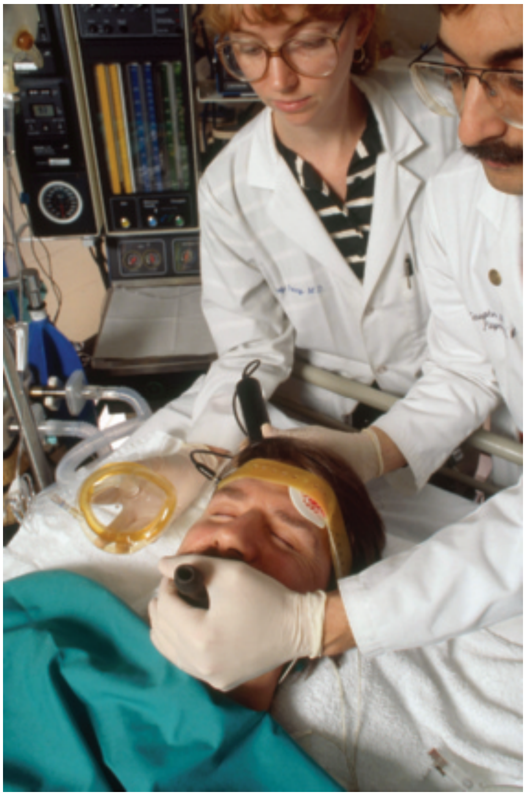
Psychiatrists had only this shaky theoretical basis for expecting ECT to be helpful for schizophrenia. When it proved to be ineffective for most cases of schizophrenia, you might guess that they would abandon it. Instead, they tried it for patients with other disorders, despite having no theoretical reason to expect it to work. Surprisingly, ECT did relieve depression in many cases. However, its misuse during the 1950s earned it a bad reputation when some patients were given ECT hundreds of times without their consent.

When antidepressant drugs became available in the late 1950s, the use of ECT declined abruptly. In the 1970s, psychiatrists brought back ECT for severely depressed patients who did not respond to the drugs. In most cases it is given only with the patient's informed consent, or if a court order requires it, such as for a patient at high risk for suicide. Ordinarily it is applied every other day for about 2 weeks. Patients are given muscle relaxants or anesthetics to minimize discomfort and the possibility of injury (Figure 14.10). The most common side effect of ECT is memory impairment, but limiting the shock to the right hemisphere reduces the memory loss. In any case, the memory impairment usually lasts only a few months, not forever (Reisner, 2003).

ECT has two advantages: It works for most patients who did not respond to other treatments (Reisner, 2003), and it acts faster than psychotherapy or standard antidepressant drugs. The main disadvantage is the high risk of relapse. The benefits are quick but usually not long-lasting. To prevent relapse, a patient periodically returns for additional ECT treatments, or follows ECT with other treatments.

Figure 14.10 Electroconvulsive therapy (ECT)

In contrast to an earlier era, ECT today is administered with muscle relaxants or anesthetics to minimize discomfort.



Will & Deni McIntyre/Science Source

Nearly a century after the introduction of ECT, no one is yet sure how it relieves depression, but like antidepressant drugs, ECT increases BDNF levels and increases the proliferation of new neurons in the hippocampus (Freire et al., 2016; Perera et al., 2007; Rocha et al., 2016). Only about 10 percent of hospitals in the United States offer ECT (Case et al., 2013).

Another option is certainly not the first thing you would try, but it is worth considering if all else fails. With **deep brain stimulation**, a physician implants a battery-powered device into the brain to deliver periodic stimulation to areas that antidepressant drugs are known to stimulate. Most patients report at least partial relief. Surgeons have to operate again when the battery runs out, usually within a year and a half (Crowell et al., 2019). Research on this technique has been limited, and it should be regarded as an experimental treatment.

Exercise and Sleep

The simplest and least expensive antidepressant treatment is a program of moderate-intensity exercise. Controlled experiments have confirmed modest antidepressant benefits, especially for people over age 60 (Bridle et al., 2012). Even just walking improves positive mood (Miller and Krizan, 2016). Exercise increases blood flow to the brain and increases the supply of nutrition to the brain.

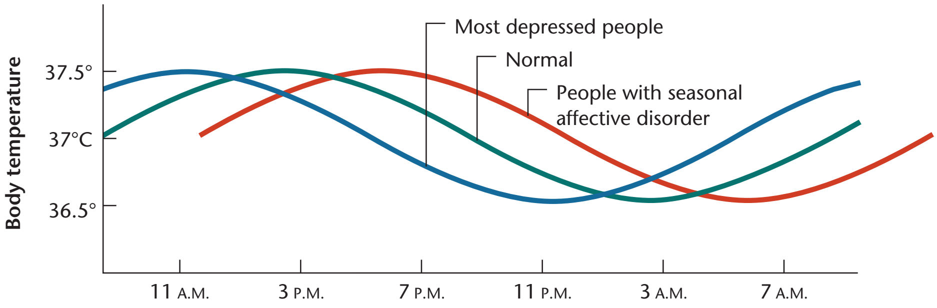
If you stay awake all night, how do you feel the next morning? Most people feel groggy and grouchy. Surprisingly, most people with depression feel better (Benedetti and Colombo, 2011). (Presumably someone discovered this therapy by accident. It's hard to imagine a logical reason to have tried it.) However, although the benefit from sleep deprivation is rapid, it is also brief, as depression usually returns after the next night's sleep.

Another approach is to alter the sleep schedule, going to bed earlier than usual. Most people with depression enter REM earlier than average and awaken early, as if they had just moved a couple time zones west. By going to bed earlier, they get a normal amount of sleep with normal timing of REM. This procedure usually relieves depression quickly and its benefits last for a week or more (Riemann et al., 1999). Eventually, however, the circadian rhythm shifts again, as if the person had traveled west again. Phase-advancing the sleep schedule has not become a popular therapy, because people have social reasons for wanting to stay awake after early evening.

Another type of sleep disorder occurs in **seasonal affective disorder (SAD)** —depression that recurs during a particular season, such as winter. SAD is most prevalent near the poles, where the winter nights are long (Haggarty et al., 2002). In contrast to most other patients with depression, who have phase-advanced circadian rhythms, people with seasonal affective disorder have phase-delayed rhythms (Teicher et al., 1997) (Figure 14.11). Many people with SAD have a mutation in one of the genes responsible for regulating the circadian rhythm (Johansson et al., 2003).

Figure 14.11 Circadian rhythms for major depression and seasonal affective disorder (SAD)

Patients with SAD are phase-delayed, whereas most other patients with depression are phase-advanced.



(**Source:** © Cengage Learning 2013)

It is possible to treat SAD with very bright lights—2,500 lux for a couple of hours each morning, or even brighter lights for a shorter time (Dallaspezia et al., 2015; Pail et al., 2011). Presumably the treatment works by resetting the circadian rhythm, although the research is not conclusive on that point. The treatment appears to be effective, usually within a week, although the research has been limited (Pjrek et al., 2020).

Stop & Check

20. What are the advantages and disadvantages of ECT?
21. What change in sleep habits sometimes relieves depression?

See page 479 for the answer.

Bipolar Disorder

Depression can be unipolar or bipolar. People with unipolar depression vary between normality and depression. People with **bipolar disorder** alternate between depression and its opposite, mania. **Mania** is characterized by restless activity, excitement, excessive self-confidence, rambling speech, and loss of inhibitions. People with full-fledged manic episodes have *bipolar I disorder*, and those with only mild, hypomanic episodes have *bipolar II disorder*. Bipolar disorder usually has its onset in the teenage years or early 20s. Figure 14.12 shows the brain's increase in glucose use during mania and its decrease during depression (Baxter et al., 1985).

Twin studies have demonstrated high heritability for bipolar disorder. At least 30 common genetic variants are linked to bipolar disorder, although no common variant has a large effect. Some of the genes linked to bipolar disorder also show a slightly positive correlation with creative accomplishments in acting, art, music, or writing (Power et al., 2015). In addition to genetics, a history of childhood maltreatment also increases the risk of bipolar disorder (McIntyre et al., 2020).

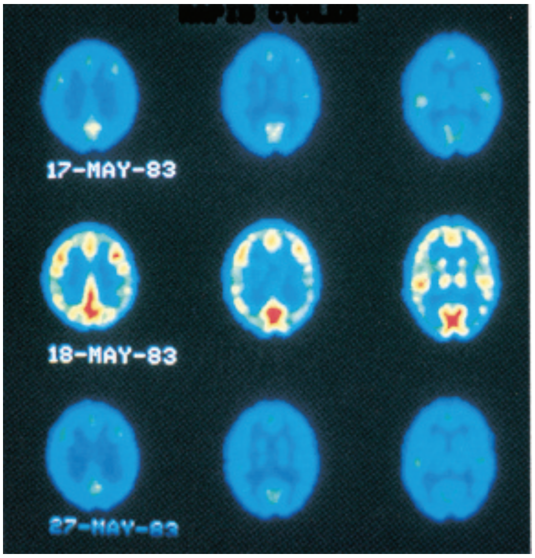
Treatments

The first successful treatment for bipolar disorder, and still the most common one, is **lithium** salts. Lithium's benefits were discovered accidentally by an Australian investigator, J. F. Cade, who believed uric acid might relieve mania and depression. Cade mixed uric acid (a component of urine) with a lithium salt to help it dissolve and then gave the solution to patients. It was indeed helpful, but investigators soon discovered that lithium was the effective agent, not uric acid.

Lithium stabilizes mood, preventing a relapse into either mania or depression. The dose must be regulated carefully, as a low dose is ineffective, and a high dose is toxic. Bipolar disorder is associated with overactivity of mitochondria, leading to hyperactivity of many neurons. A likely hypothesis for the effectiveness of lithium is that it

Figure 14.12 PET scans for a patient with bipolar disorder

Horizontal planes through three levels of the brain are shown for each day. On May 17 and May 27, when the patient was depressed, brain metabolic rates were low. On May 18, when the patient was in a cheerful, hypomanic mood, the brain metabolic rate was high. Red indicates the highest metabolic rate, followed by yellow, green, and blue.



(**Source:** "Cerebral metabolic rates for glucose in mood disorders," by L. R. Baxter, M. E. Phelps, J. C. Mazziotta, J. M. Schwartz, R. H. Gerner, C. E. Selin, et al., 1985, *Archives of General Psychiatry, 42*, 441–447.)

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reduces the hyperactivity (Kato, 2019). Other drugs are the anticonvulsants valproate and carbamazepine, which also reduce overexcitation.

Patients with bipolar disorder frequently have poor sleep quality during manic phases, depressed phases, and even when their mood is normal (Altena et al., 2016). Getting consistent, adequate sleep helps stabilize mood and decrease the risk of a new episode (Harvey et al., 2009).

Stop & Check

22. What are common treatments for bipolar disorder?

See page 479 for the answer.

Module 14.2 | In Closing

The Biology of Mood Swings

There is nothing abnormal about feeling sad after a bad experience. For people with major depression or bipolar disorder, mood becomes largely independent of events. Depression persists despite good news, and mania produces self-confidence that no contradiction can deter. Studying these states informs us about the brain states that correspond to moods.

Summary

1. People with major depression find that almost nothing makes them happy. Depression generally occurs as a series of episodes. **470**
2. The usual sleep pattern of people with depression is early onset of REM sleep and early awakening. **471**
3. Depression has a genetic predisposition, but no common variant has a strong effect by itself. Early-onset and late-onset depression appear to be associated with different genes. **471**
4. Stress can provoke depression by activating the immune system. **472**
5. Tricyclics block reuptake of serotonin and catecholamines. SSRIs block reuptake of serotonin. SNRIs block reuptake of both serotonin and norepinephrine. MAOIs block an enzyme that breaks down catecholamines and serotonin. However, these effects do not fully explain their benefits. **472**
6. Antidepressant drugs facilitate a receptor for the neurotrophin BDNF. Because the standard antidepressants attach weakly, they have to accumulate in the brain for weeks to reach an effective concentration. **473**
7. On average, standard antidepressant drugs are only moderately more effective than placebos. **474**
8. Limited research indicates that psychedelic drugs can produce strong and rapid effects in many cases, because they attach more strongly to the receptor for BDNF. However, they risk producing hallucinations, delusions, or addiction. **474**
9. Psychotherapy is more likely than antidepressant drugs to produce long-lasting benefits. **475**
10. Other therapies for depression include electroconvulsive therapy, deep brain stimulation, exercise, and sleep alterations. **475**
11. People with bipolar disorder alternate between depression and mania. Effective therapies include lithium salts and certain anticonvulsant drugs. A consistent sleep schedule is also recommended. **477**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

atypical antidepressants	**473**
bipolar disorder	**477**
deep brain stimulation	**476**
electroconvulsive therapy (ECT)	**475**
lithium	**477**
major depression	**470**
mania	**477**
monoamine oxidase inhibitors (MAOIs)	**473**
psychedelics	**474**
seasonal affective disorder (SAD)	**476**
selective serotonin reuptake inhibitors (SSRIs)	**472**
serotonin norepinephrine reuptake inhibitors (SNRIs)	**472**
tricyclics	**472**

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Thought Questions

1. Some people have suggested that ECT relieves depression by causing people to forget the events that caused it. What evidence opposes this hypothesis?
2. Suppose a person with depression rides a cruise ship that travels around the world, one time zone west every day or two. What effect, if any, would you expect on the depression, and why?

Stop & Check Answers

10. Most depressed people enter REM sleep sooner than average and awaken early.
11. A gene that might produce measurable effects in one population might be rare or absent from another population.
12. Relatives of people with early-onset depression have a high risk of other psychological disorders. Relatives of people with late-onset depression have a high probability of circulatory problems.
13. Tricyclic drugs block reuptake of serotonin and catecholamines. They also block histamine receptors, acetylcholine receptors, and certain sodium channels, thereby producing unpleasant side effects.
14. SSRIs selectively inhibit the reuptake of serotonin.
15. MAOIs block the enzyme MAO, which breaks down catecholamines and serotonin. The result is increased availability of these transmitters.
16. Antidepressants attach relatively weakly to the receptor for BDNF. They accumulate slowly in the brain until they reach a high enough concentration to be effective.
17. If someone's BDNF receptor is already functioning well, further facilitation may produce little effect.
18. For more severe cases, the percentage of patients who improve remains about the same for patients taking antidepressant drugs, but fewer patients taking placebos show improvement.
19. Psychotherapy produces no side effects. Also, people who respond well to psychotherapy have a lower risk of later relapse than people who respond to antidepressant drugs.
20. ECT helps many people who do not respond to other treatments, and its benefits usually develop quickly, but the probability of a quick relapse is high.
21. Going to bed earlier sometimes relieves depression
22. The common pharmaceutical treatments for bipolar disorder are lithium salts and certain anticonvulsant drugs—valproate and carbamazepine. A consistent sleep schedule is also recommended.

Module 14.2 | End-of-Module Quiz

1. Why has laboratory research on depression sometimes led to misleading results?
   - **a.** Researchers took the average from separate studies.
   - **b.** Researchers published the means without including the standard deviations.
   - **c.** Researchers studied only juvenile animals.
   - **d.** Researchers studied only male animals.

2. Relatives of people with late-onset depression have an increased probability of what type of disorder?
   - **a.** Anxiety disorders
   - **b.** Circulatory problems
   - **c.** Alcohol abuse
   - **d.** Migraine headaches

3. When the immune system releases cytokines, what do the cytokines produce?
   - **a.** Inactivity and loss of appetite
   - **b.** Increased sensitivity to bright lights
   - **c.** Manic or hypomanic mood
   - **d.** Decreased body temperature

4. How do SSRIs differ from tricyclic antidepressants?
   - **a.** SSRIs act on one type of synapse instead of several.
   - **b.** SSRIs act on the hippocampus instead of the cerebral cortex.
   - **c.** SSRIs enter the brain more rapidly and remain there longer.
   - **d.** SSRIs are chemically similar to the brain's own neurotransmitters.

5. If someone starts taking antidepressant drugs, when do behavioral benefits emerge?
   - **a.** As soon as the drug reaches the brain
   - **b.** As soon as the drug attaches to receptors on the synapses
   - **c.** About one day after taking the first dose
   - **d.** Two weeks or more after starting treatment

6. Standard antidepressants take effect only after their brain concentration builds up enough to do what?
   - **a.** Facilitate the receptors for BDNF
   - **b.** Increase the concentration of serotonin in the synaptic cleft
   - **c.** Increase the production of cytokines
   - **d.** Shift blood flow from the left hemisphere to the right hemisphere

7. If several patients who did not respond to drug A later improve after switching to drug B, what conclusion, if any, follows?

- **a.** Drug B is more effective than drug A.
- **b.** Some people respond to drug B but not to drug A.
- **c.** Any switch in drugs increases patients' motivation and therefore helps them recover.
- **d.** None of these conclusions follows.

8. Why is the use of psychedelics more expensive than standard antidepressant drugs?

- **a.** They must be administered under careful supervision.
- **b.** The drug companies' patents on these drugs are recent.
- **c.** They must be administered daily instead of weekly.
- **d.** They are still illegal in most places.

9. Relative to other treatments, what is the advantage of psychotherapy?

- **a.** It affects the mind and not the brain.
- **b.** It is the most likely to produce rapid benefits.
- **c.** It is the most likely to produce long-lasting benefits.
- **d.** It is the least expensive.

10. Which of these is most often recommended for seasonal affective disorder?

- **a.** Going to sleep hours later than usual
- **b.** Exposure to bright lights in the morning
- **c.** Eating a fat-free diet
- **d.** Soothing music throughout the night

11. Which of these is a common treatment for bipolar disorder?

- **a.** Lithium salts
- **b.** Uric acid
- **c.** Vitamin C
- **d.** Avoidance of gluten

Answers: 1d, 2b, 3a, 4a, 5d, 6a, 7d, 8a, 9c, 10b, 11a.

Module 14.3

Schizophrenia

Learning Objectives

After studying this module, you should be able to:

10. List the symptoms of schizophrenia, distinguishing between positive and negative symptoms.
11. Describe and evaluate the research on genetic predispositions to schizophrenia.
12. Discuss the environmental contributors and the two-hit hypothesis.
13. Discuss the treatments for schizophrenia and their limitations.

Here is a conversation between two people diagnosed with schizophrenia:

> **A:** Do you work at the air base?
>
> **B:** You know what I think of work. I'm 33 in June, do you mind?
>
> **A:** June?
>
> **B:** 33 years old in June. This stuff goes out the window after I live this, uh—leave this hospital. So I can't get my vocal cords back. So I lay off cigarettes. I'm in a spatial condition, from outer space myself. . . .
>
> **A:** I'm a real spaceship from across.
>
> **B:** A lot of people talk that way, like crazy, but "Believe It or Not," by Ripley, take it or leave it—alone—it's in the *Examiner,* it's in the comic section, "Believe It or Not," by Ripley, Robert E. Ripley. Believe it or not, but we don't have to believe anything, unless I feel like it. Every little rosette—too much alone.
>
> **A:** Yeah, it could be possible.
>
> **B:** I'm a civilian seaman.
>
> **A:** Could be possible. I take my bath in the ocean.
>
> **B:** Bathing stinks. You know why? 'Cause you can't quit when you feel like it. You're in the service. (Haley, 1959, p. 321)

People with schizophrenia say and do things that other people (including other people with schizophrenia) find difficult to understand. Both biological and environmental factors contribute.

Diagnosis

In 1911, Eugen Bleuler introduced the term **schizophrenia**. Although the term is Greek for *split mind*, it does *not* mean an alternation among personalities. What Bleuler meant by schizophrenia was a split between the emotional and intellectual aspects of experience: Someone might giggle or cry for no apparent reason or react inappropriately to good or bad news. Detachment of emotion from intellect is no longer considered a central feature of schizophrenia, but the term lives on. The best estimate is that about 7 to 8 people per 1,000 will develop schizophrenia at some point in life (Saha et al., 2005). It occurs in all ethnic groups and all parts of the world, but in some countries more than others, and somewhat more often in men than in women. Because schizophrenia often produces long-term debilitation with onset in young adulthood, it is a major health problem in terms of the loss of productive, enjoyable years of life.

Although the first diagnosis of schizophrenia usually occurs in early adulthood, mild problems usually begin in childhood, including deficits in attention, memory, and impulse control (Keshavan et al., 2005). An analysis of home movies found that people who later developed schizophrenia showed movement abnormalities during infancy (Walker et al., 1994).

The original term for schizophrenia was *dementia praecox,* Latin for "premature mental deterioration." Originally, psychiatrists considered schizophrenia a *progressive* disorder—that is, one that progresses to worse and worse outcomes over time, analogous to Parkinson's disease or Alzheimer's disease. That conclusion formed during an era when patients with schizophrenia were confined to large, poorly staffed mental hospitals that offered no effective treatment and sometimes abusive treatment. Under those circumstances, gradual deterioration was almost inevitable. The more recent experience is that most people remain at a more-or-less constant level, but some alternate between remission and relapse, and some have a single episode and then recover (Hui et al., 2019; Lally et al., 2017; Zipursky et al., 2013).

According to *DSM-5*, the *Diagnostic and Statistical Manual, 5th edition* (American Psychiatric Association, 2013), to be diagnosed with schizophrenia, someone must have deteriorated in everyday functioning (work, interpersonal relations, self-care) for at least 6 months for reasons not attributable to other disorders. The person must also have at least two symptoms from the following list, including at least one of the first three:

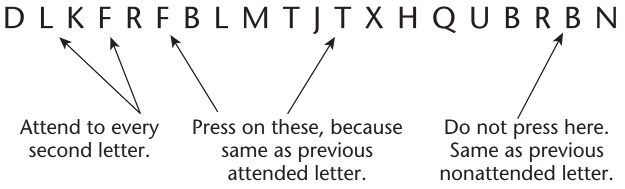
- **Delusions** (unjustifiable beliefs, usually of a social nature, such as "Beings from outer space are controlling my actions")
- **Hallucinations** (false sensory experiences, such as hearing voices when alone)
- Disorganized speech (rambling or incoherent)
- Grossly disorganized behavior
- Weak emotional expression, speech, and socialization

Diagnosis is sometimes difficult. An apparent delusion ("People are persecuting me") might be true. Many healthy people have occasionally heard a voice when they knew they were alone. The phrase "grossly disorganized behavior" encompasses a wide variety of possibilities. Two people diagnosed with schizophrenia might have almost nothing in common. The genetics vary among people diagnosed with schizophrenia, and so do the brain abnormalities. We are probably dealing with a family of related conditions, rather than a single disorder.

The first four items on the list—delusions, hallucinations, disorganized speech, and disorganized behavior—are called **positive symptoms**, meaning behaviors that are present that should be absent. Weak emotional expression, speech, and socialization are **negative symptoms**—absent behaviors that should be present. Negative symptoms are generally stable over time and difficult to treat.

Although *DSM-5* does not list cognitive symptoms as essential to the diagnosis, cognitive impairments are common in schizophrenia. The most common cognitive impairments are slow processing speed, impaired long-term memory, difficulty perceiving others' emotions from their facial expressions and body language, and errors in perceiving others' intentions and beliefs (Green et al., 2019). Attention problems are common also (Lakatos et al., 2013). The cognitive impairments usually remain stable throughout life, even in people who show recovery from the positive symptoms. The cognitive impairments correlate with lower-than-average heart rate variability, which implies abnormal functioning of the autonomic nervous system (Haigh et al., 2021).

One hypothesis is that impairments of attention and working memory are the central problem. One way to test this idea is to see whether we could make normal, healthy people talk or behave in incoherent ways if we overtaxed their working memory. Imagine yourself in the following study. A researcher shows a series of pictures for 30 seconds each, and you are supposed to tell a short story about each one. If you see a picture again, you should tell a new story about it, unlike your first one. You have an additional task to burden your working memory: While you are telling stories, letters appear on the screen, one at a time. You should pay attention to every second letter. Whenever it is the same as the last letter that you attended to, you should press a key. For example,


D L K F R F B L M T J T X H Q U B R B N
Attend to every second letter.
Press on these, because same as previous attended letter.
Do not press here. Same as previous nonattended letter.

Most people's speech becomes less clear when they perform this memory task while trying to tell a story. If it is the second presentation of a picture, requiring them to avoid what they said the first time and tell a totally new story, the memory task causes even greater interference, and speech becomes incoherent, much like schizophrenic speech (Kerns, 2007). The implication is that a limitation of working memory could explain several aspects of schizophrenia.

In addition to the defining symptoms, researchers have reported unexplained oddities that are characteristic of many people with schizophrenia:

- A higher-than-average probability of autoimmune diseases such as Guillain-Barré syndrome or pernicious anemia (Benros et al., 2014).
- An increased risk of colon cancer but a decreased risk of several other types of cancer, rheumatoid arthritis, and allergies (Goldman, 1999; Hippisley-Cox et al., 2007; Roppel, 1978; Rubinstein, 1997; Tabarés-Seisdedos and Rubenstein, 2013).
- A characteristic body odor, attributed to the chemical *trans*-3-methyl-2-hexenoic acid, and a decreased ability to smell that chemical (Brewer et al., 2007; Smith et al., 1969).
- Deficits in pursuit eye movements—the ability to keep the eyes on a moving target (Keefe et al., 1997; Sereno and Holzman, 1993).
- A tendency for women who have a schizophrenic breakdown during pregnancy to give birth to daughters, and for women who have a breakdown shortly after giving birth to have given birth to sons (Taylor, 1969).

Stop & Check

23. Why are hallucinations considered a positive symptom?

See page 490 for the answer.

Differential Diagnosis of Schizophrenia

In the description for diagnosing schizophrenia, did you notice the expression "not attributable to other disorders"? Even if someone's symptoms clearly match the description of schizophrenia, a therapist must make a **differential diagnosis**—that is, one that rules out other

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conditions. Here are a few conditions that sometimes resemble schizophrenia:

- *Substance abuse*: Abuse of amphetamine, methamphetamine, cocaine, or psychedelics can produce hallucinations or delusions. Substance abuse is more likely than schizophrenia to produce visual hallucinations.
- *Brain damage*: Damage or tumors in the temporal or prefrontal cortex can produce some of the symptoms of schizophrenia.
- *Uncorrected hearing deficits*: Someone with impaired hearing might think that everyone else is whispering and worries, "They're whispering about me!" Delusions of persecution can develop.
- *Huntington's disease*: The symptoms of Huntington's disease include hallucinations, delusions, and disordered thinking, as well as motor symptoms. An uncommon type of schizophrenia, *catatonic schizophrenia,* includes motor abnormalities. A mixture of psychological and motor symptoms could represent either schizophrenia or Huntington's disease.
- *Nutritional problems*: Niacin deficiency can produce hallucinations and delusions (Hoffer, 1973). Schizophrenic symptoms can also arise from allergies to gluten or milk proteins, or from pathogens that irritate the digestive tract (Severance et al., 2016).

Genetic Influences

Huntington's disease depends on a single gene. Examining chromosome 4 can reveal with almost perfect accuracy whether someone will or will not develop the disease. Although schizophrenia and other psychiatric disorders have high heritability, they do not depend on any single gene.

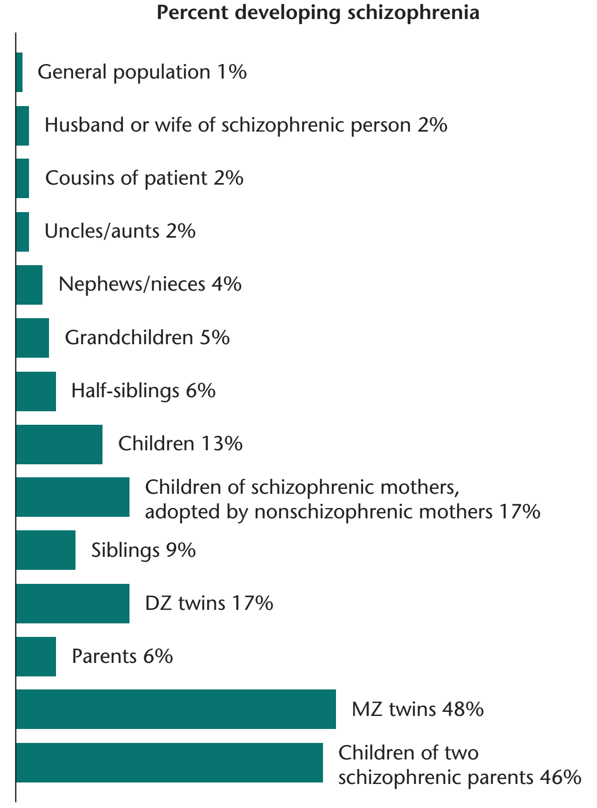
Family Studies

The more closely you are biologically related to someone with schizophrenia, the greater your own probability of schizophrenia, as shown in Figure 14.13 (Gottesman, 1991). One of the most important points in Figure 14.13 is that monozygotic twins have a higher **concordance** (agreement) for schizophrenia than do dizygotic twins. Furthermore, twin pairs who are monozygotic but thought they weren't, are more concordant than twin pairs who thought they were, but really aren't (Kendler, 1983). That is, *being* monozygotic is more important than *being treated as* monozygotic.

The high concordance for monozygotic twins has long been taken as strong evidence for a genetic influence. However, note that monozygotic twins have only about 50 percent concordance, and some studies show even less (Hilker et al., 2018). Also note the greater similarity between dizygotic twins than between siblings in Figure 14.13. Dizygotic twins have the same genetic resemblance as siblings but greater environmental similarity, including prenatal environment.

Figure 14.13 Probabilities of developing schizophrenia

People with closer genetic relationships have higher concordance for schizophrenia.



(**Source:** Based on data from Gottesman, 1991)

Adopted Children Who Develop Schizophrenia

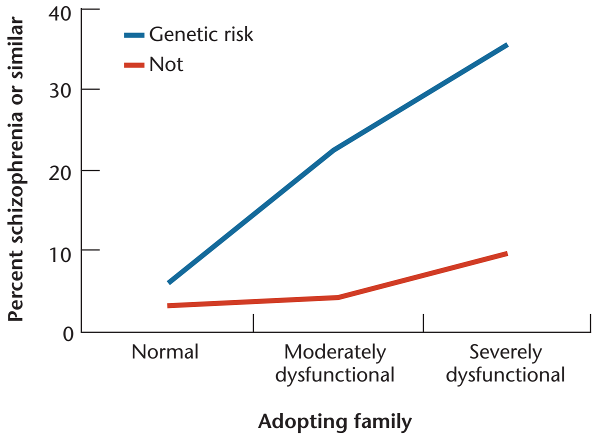
For adopted children who develop schizophrenia, the disorder is more common in their biological relatives than their adopting relatives. A Danish study found schizophrenia in 12.5 percent of the immediate biological relatives and none of the adopting relatives (Kety et al., 1994). Note in Figure 14.13 that children of a mother with schizophrenia have a moderately high probability of schizophrenia, even if adopted by mentally healthy parents.

The adoption results suggest a genetic basis, but they are also consistent with a prenatal influence. A pregnant woman with schizophrenia passes her genes to her child, but she also provides the prenatal environment. Many women with schizophrenia abuse alcohol or other drugs, eat a poor diet, and have complications during pregnancy and delivery (Jablensky et al., 2005). When their children develop schizophrenia, we cannot be sure that the reason is genetic.

A study of adopted children in Finland found a high probability of schizophrenia or related conditions among

Figure 14.14 Probability of schizophrenia or similar conditions in adopted children

The probability was higher for children of a mother with schizophrenia, but growing up in a dysfunctional family magnified that risk.



(**Source:** Based on data from Wynne et al., 2006)

children who had a biological mother with schizophrenia *and* a severely disordered adopting family. The genetic risk itself or the disordered family itself had less effect, as shown in Figure 14.14 (Wynne et al., 2006).

Identified Genes

Researchers working with various populations have identified hundreds of genetic loci that differ on average between people with or without schizophrenia, including many that code for proteins in the brain (Jaffe et al., 2018; Trubetskoy et al., 2022). The results vary from one study to another, partly because some genes are common in one ethnic group but not in another (Vieland et al., 2014).

No common genetic variant produces more than a small increase in the probability of schizophrenia. Indeed, it would be difficult for any gene with a strong link to schizophrenia to become common, because people with schizophrenia have, on average, fewer than half as many children as other people do, and their brothers and sisters do not compensate by having more children than average (Bundy et al., 2011). A few rare genes are known to greatly increase the risk of schizophrenia, mostly by disrupting the development of glutamate synapses or by interfering with the immune system (Lencz et al., 2021; Purcell et al., 2014; Singh et al., 2022). Certain genes are described as "intolerant of loss of function." Geneticists only occasionally find variants in those genes because the variants decrease survival or reproduction. Nevertheless, many such variants occur in people with schizophrenia (Rees et al., 2020). The common genes producing a small risk and the rare genes causing a greater risk mostly affect the same brain functions, just to different degrees (Trubetskoy et al., 2022).

One common gene related to schizophrenia alters the major histocompatibility complex—that is, genes controlling cell surface proteins that the immune system recognizes (Kim et al., 2021). Another important gene, called ***DISC1** (disrupted in schizophrenia 1)*, controls differentiation and migration of neurons in brain development (Ishizuka et al., 2011; Steinecke et al., 2012), production of dendritic spines (Hayashi-Takagi et al., 2010), the generation of new neurons in the hippocampus (Duan et al., 2007), and learning (Greenhill et al., 2015).

Another genetic contributor is **microdeletion**, the loss of a small part of a chromosome (Bergen et al., 2019). Even a tiny deletion of a critical segment can lead to cognitive dysfunction and symptoms of schizophrenia (Zaremba et al., 2017). Thus, the current consensus is that many common genetic variants slightly increase the probability of schizophrenia, and a new mutation or microdeletion of a critical gene can greatly increase the probability. A genetic predisposition then interacts with environmental triggers.

Stop & Check

24. Why are the results about adopted children with schizophrenia ambiguous with regard to the role of genetics?
25. Given that no common gene has a strong relationship to schizophrenia, how else can we explain the high heritability?

See page 490 for the answer.

Environmental Influences

According to the **neurodevelopmental hypothesis**, prenatal or neonatal difficulties—of either genetic or environmental origin—can produce abnormalities in the developing brain that predispose to schizophrenia (Weinberger, 1996). Brain abnormalities occurring in infancy might not show their full effects until later. The dorsolateral prefrontal cortex, an area often impaired in schizophrenia, is one of the slowest brain areas to mature. When researchers damaged it in infants, the monkeys' behavior was nearly normal at age 1 year, but worse at age 2 years (Goldman, 1971, 1976). Presumably, the effects of brain damage were minimal at age 1 year because the dorsolateral prefrontal cortex doesn't do much at that age anyway. Later, when it should begin assuming important functions, the damage makes a difference (Figure 14.15).

Another way to explain the relationship between early impairment and later symptoms is the **two-hit hypothesis**. According to this proposal, schizophrenia is the result of a combination of a genetic predisposition and impacts from the environment in prenatal/neonatal development, later in life, or both (Bayer et al., 1999).

Prenatal or Early Postnatal Factors

The risk of schizophrenia is mildly elevated among people who had problems that could affect early brain development, including poor prenatal nutrition, premature birth, low birth

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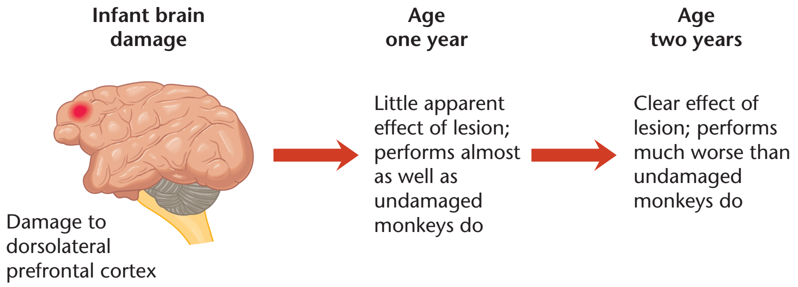
Figure 14.15 Delayed effects of brain damage in infant monkeys

After damage to the dorsolateral prefrontal cortex, monkeys are unimpaired at age 1 year but impaired later, when this area ordinarily matures. Researchers speculate that similar damage in humans might produce behavioral deficits not apparent until adulthood.


Infant brain damage
Age one year
Age two years
Little apparent effect of lesion; performs almost as well as undamaged monkeys do
Clear effect of lesion; performs much worse than undamaged monkeys do
Damage to dorsolateral prefrontal cortex

(**Source:** Based on P. S. Goldman, 1976)

weight, and complications during delivery (Ballon et al., 2007). The risk also increases if the mother was exposed to extreme stress, such as the sudden death of a close relative, early in her pregnancy (Khashan et al., 2008) or if the mother had almost any prolonged illness during pregnancy (Brown, 2011).

Related evidence comes from the **season-of-birth effect**, the tendency for people born in winter to have a slightly increased probability of developing schizophrenia. This tendency is more pronounced in latitudes far from the equator (Davies et al., 2003; Torrey et al., 1997). The leading hypothesis to explain this effect is viral infection. Influenza and other viral epidemics are common in the fall. Therefore, the reasoning goes, many pregnant women become infected in the fall with a virus that impairs a crucial stage of brain development in a baby who will be born in the winter or early spring. Researchers retrieved blood samples that hospitals had taken from pregnant women and stored for decades. They found increased incidence of influenza virus among mothers whose children eventually developed schizophrenia (Brown et al., 2004; Buka et al., 2001). Even if the virus itself does not cross the placenta into the fetus's brain, the mother's cytokines (part of the immune system) do cross, and excessive cytokines can impair brain development (Zuckerman et al., 2003). The mother's infection also causes a fever, which slows the division of fetal neurons (Estes and McAllister, 2016). (Exercise during pregnancy does not overheat the abdomen and is not dangerous to the fetus. Hot baths and saunas pose a possible risk, however.) A prenatal immune reaction can also activate microglia that impair mitochondria and synapse formation (Park et al., 2020).

If a mother is Rh-negative and her baby is Rh-positive, the baby's Rh-positive blood factor may trigger an immunological rejection by the mother. The response is weak with the woman's first Rh-positive baby but stronger in later pregnancies, and it is more intense with boy than girl babies. Second- and later-born boy babies with Rh incompatibility have an increased risk of hearing deficits, cognitive deficits, and schizophrenia (Hollister et al., 1996).

Each of these early factors correlates only slightly with schizophrenia. By themselves, none has a big effect, but they can combine with genetics or later insults.

Factors Later in Life

Physical, emotional, or sexual abuse during childhood increases the risk and the probable severity of later schizophrenia (Ingeç and Kiliçaslan, 2020). Traumatic experiences early in life impair the ability of the hypothalamus-pituitary-adrenal axis to produce its usual negative feedback relationship. As a result, any stress reaction later in life is prolonged. The effect is exaggerated in people with a genetic predisposition to a strong stress reaction (Stramecki et al., 2020).

Many studies report that living in a crowded city correlates with schizophrenia. Urban environments are associated with decreased sunlight, increased air pollution, and other factors that might contribute to vulnerability, but it is also possible that people at risk of schizophrenia tend to move to big cities (Colodro-Conde et al., 2018). The incidence of schizophrenia is also elevated among people who immigrate from one country to another (Robinson and Bergen, 2021). Entering a new country with different language, customs, and diet can be stressful in many ways, in addition to the potential for encountering unfair discrimination.

Schizophrenia has also been linked to childhood head injuries in early childhood (AbdelMalik et al., 2003), exposure to the Borna disease virus (Azami et al., 2018), and infection with the parasite *Toxoplasma gondii*. This parasite reproduces only in cats, but people can be exposed to it by handling infected cats, by playing in soil or sand where cats have defecated, or by eating chicken or pork after those animals were fed in infected soil. The parasite does not always cross into the human brain, but if it does, it impairs a child's brain development (Kramer and Bressan, 2015; Sutterland et al., 2015; Yolken et al., 2009).

Stop & Check

26. Why do researchers favor the two-hit hypothesis?

See page 490 for the answer.

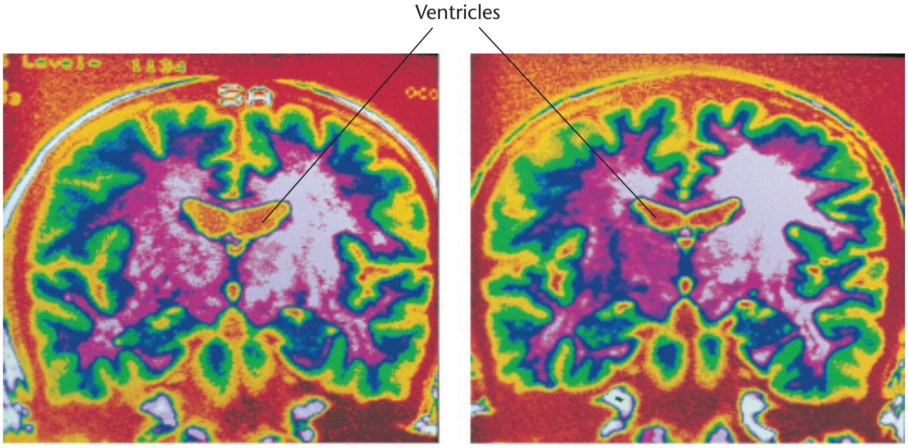
Brain Abnormalities

Many people with schizophrenia show mild abnormalities of brain anatomy, including less-than-average gray matter in the frontal cortex, hippocampus, and other areas (Gallardo-Ruiz et al., 2019; Osimo et al., 2019; van Erp et al., 2016). White matter is reduced also, and the ventricles (fluid-filled spaces within the brain) are enlarged (Kochunov and Hong, 2014;

Meyer-Lindenberg, 2010; Wolkin et al., 1998; Wright et al., 2000) (Figure 14.16). Several connections among brain areas are weaker than average (Cumming et al., 2021). However, the brain abnormalities are highly variable, and mild in most cases (Kuo and Pogue-Geile, 2019; Woodward, 2016). Most of the brain abnormalities are present at the time of first diagnosis, with only slight deterioration after the first few years (Andreasen et al., 2011; Chiapponi et al., 2013; Nesvag et al., 2012; Vita, De Peri et al., 2012; Woodward, 2016). Even when further deterioration does occur, it could be a result of drug abuse (common in people with schizophrenia) rather than a result of schizophrenia itself (Stoychev, 2019).

Figure 14.16 Coronal sections for identical twins

The twin on the left has schizophrenia; the twin on the right does not. The ventricles (near the center of each brain) are larger in the twin with schizophrenia.



Photos courtesy of E. F. Torrey & M. F. Casanova/NIMH

One area frequently found to be impaired is the prefrontal cortex. As you might predict, people with schizophrenia perform poorly at tasks that depend on the prefrontal cortex (Goldberg et al., 1987; Rapado-Castro et al., 2021; Spindler et al., 1997). An example of a task that tests for damage to the prefrontal cortex is the Wisconsin Card Sorting Test. Suppose someone hands you a shuffled deck of cards that differ in number, color, and shape of objects—for example, the first three cards might show two red circles, five blue triangles, and four green squares. First, you should sort the cards by color. Then the rule changes, and you are supposed to sort them by number, and later by shape. Shifting to a new rule requires you to suppress the old one and activate your prefrontal cortex (Konishi et al., 1998). People with damage to the prefrontal cortex have no trouble following whichever rule comes first, but they have trouble shifting to a new rule. Most people with schizophrenia have the same difficulty.

Stop & Check

27. If brain abnormalities usually do not grow worse over time, what is the implication for the idea that schizophrenia is a progressive disorder?

See page 490 for the answer.

Treatments

Before antipsychotic drugs became available in the mid-1950s, most people with schizophrenia were indefinitely confined to mental hospitals. Today, effective drugs and outpatient treatment offer more hope.

Antipsychotic Drugs and Dopamine

In the 1950s, psychiatrists discovered that **chlorpromazine** (trade name Thorazine) relieves the positive symptoms of schizophrenia for most patients. Other **antipsychotic, or neuroleptic, drugs** (drugs that tend to relieve schizophrenia and similar conditions) occur in two chemical families: the **phenothiazines** (FEE-no-THI-uh-zeens), which include chlorpromazine, and the **butyrophenones** (BYOO-tir-oh-FEE-noans), which include haloperidol (trade name Haldol). Behavioral benefits of any of these drugs develop gradually over weeks, as the drug gradually accumulates in the synapses. About 20 percent of patients can stop taking the drugs after a first episode without a return of symptoms. For other patients, the choice is between continuing with the drug or risking a relapse. With long-term use, the side effects increase, and the effectiveness against schizophrenia often decreases (Chestnyk et al., 2021; Sommer et al., 2019).

Each of these drugs blocks dopamine synapses, specifically type D_2 receptors. For each drug, researchers determined the mean dose prescribed for patients with schizophrenia (displayed along the horizontal axis) and the amount needed to block dopamine receptors (displayed along the vertical axis). As Figure 14.17 shows, the drugs that are most effective against schizophrenia (and therefore used in the smallest doses) are the most effective at blocking dopamine receptors (Seeman et al., 1976).

That finding inspired the **dopamine hypothesis of schizophrenia,** which holds that schizophrenia results from excess activity at dopamine synapses in certain brain areas. Although the concentration of dopamine in the brain is no higher than normal, dopamine release is increased in the basal ganglia, especially in response to stressful events (Howes and Kapur, 2009; Simpson et al., 2010). Further support for the dopamine hypothesis comes from the fact

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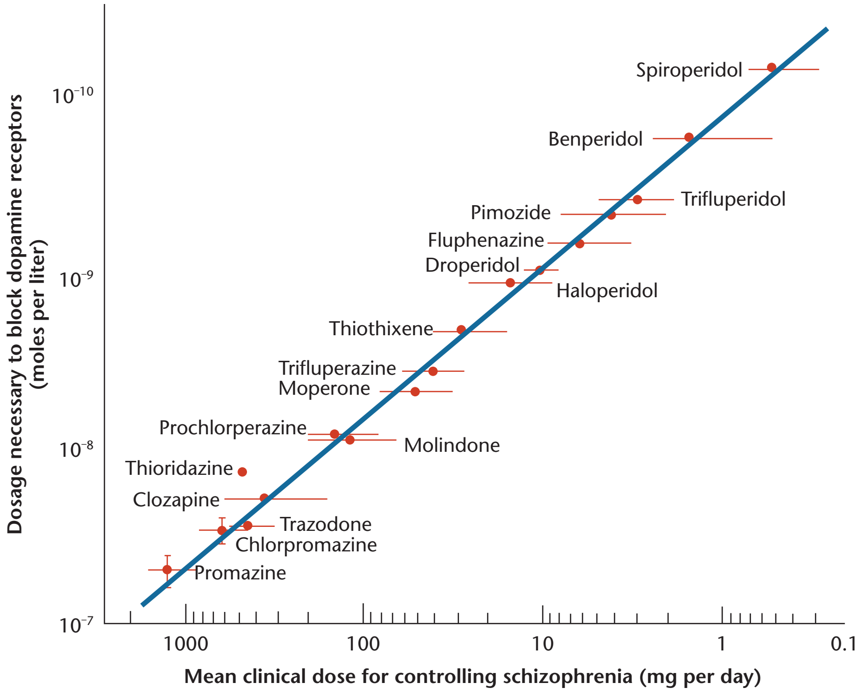
Figure 14.17 Dopamine-blocking effects of antipsychotic drugs

Drugs are arranged along the horizontal axis in terms of the average daily dose prescribed for patients with schizophrenia. (Horizontal lines indicate common ranges.) *Larger* doses are to the left, and *smaller* doses are to the right so that *more effective* drugs are to the right. Along the vertical axis is a measurement of the amount of each drug required to achieve a certain degree of blockage of postsynaptic dopamine receptors. *Larger* doses are toward the bottom, and *smaller* doses are toward the top so that the drugs on top are *more effective*.



Source: From "Antipsychotic drug doses and neuroleptic/dopamine receptors," by P. Seeman, T. Lee, M. Chau-Wong, and K. Wong, 1976, *Nature, 261,* 717–719. Copyright © 1976 Macmillan Magazines Limited. Reprinted by permission of Nature and Phillip Seeman.

that abuse of amphetamine, methamphetamine, or cocaine (which all increase dopamine at the synapses) can induce **substance-induced psychotic disorder,** characterized by hallucinations and delusions.

In a clever study, researchers measured the number of dopamine receptors occupied at a given moment. They used a radioactively labeled drug, IBZM, that binds to type D_2 receptors. Because IBZM binds only to receptors that dopamine did not already bind, measuring the radioactivity counts the number of vacant dopamine receptors. Then the researchers used a second drug, AMPT, that blocks all synthesis of dopamine and again used IBZM to count the number of vacant D_2 receptors. Because AMPT had prevented production of dopamine, *all* D_2 receptors should be vacant at this time, so the researchers got a count of the total. Then they subtracted the first count from the second count, yielding the number of D_2 receptors occupied by dopamine at the first count. The people with schizophrenia had about twice as many D_2 receptors occupied as normal:

- First count: IBZM binds to all D_2 receptors not already attached to dopamine.
- Second count: IBZM binds to all D_2 receptors (because AMPT eliminated production of dopamine).
- Second count minus first count equals the number of D_2 receptors bound to dopamine at the first count. (Abi-Dargham et al., 2000)

Stop & Check

28. The ability of first-generation antipsychotic drugs to relieve schizophrenia correlates strongly with what effect on neurotransmitters?

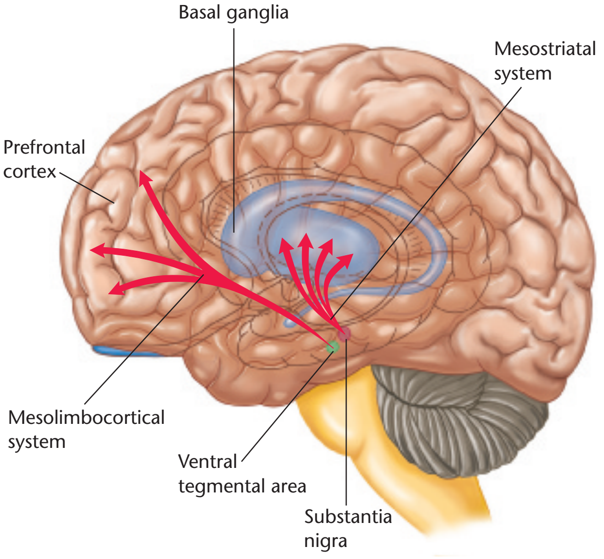
See page 490 for the answer.

Newer Antipsychotic Drugs

The brain has several dopamine pathways with different functions (Figure 14.18). Drugs that block dopamine synapses produce their benefits by acting on neurons in the **mesolimbocortical system,** neurons that project from the midbrain to the limbic system and prefrontal cortex. However, these drugs also block dopamine neurons in the *mesostriatal system* that projects to the basal ganglia, and in doing so they produce **tardive dyskinesia** (TARD-eev dis-kih-NEE-zhee-uh), characterized by tremors and other involuntary movements (Kiriakakis et al., 1998).

Figure 14.18 Two major dopamine pathways

Blocking the mesolimbocortical system helps to relieve the symptoms of schizophrenia. Blocking the path to the basal ganglia produces tardive dyskinesia, a movement disorder.

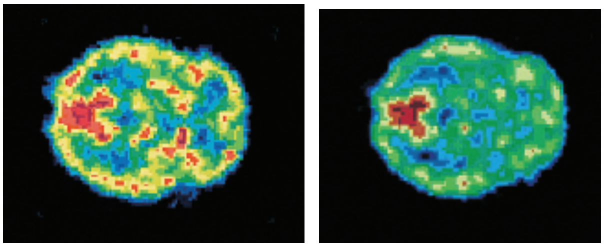


(**Source:** Adapted from Valzelli, 1980)

Once tardive dyskinesia emerges, it persists long after someone quits the drug (Kiriakakis et al., 1998). Drugs called **second-generation antipsychotics**, or *atypical antipsychotics,* relieve schizophrenic symptoms with less risk of movement problems (Carbon et al., 2017) (Figure 14.19). The most common of these drugs are clozapine and risperidone. Compared to drugs like haloperidol, the second-generation antipsychotics have less effect on dopamine receptors, but they also increase the release of glutamate (Melone et al., 2001). Unfortunately, they produce other side effects, including weight gain and impairment of the immune system. Studies have disagreed about whether the second-generation antipsychotics improve quality of life more than the original drugs do (Grunder et al., 2016; Jones et al., 2006). Third-generation antipsychotic drugs, which act mainly at dopamine type 2 receptors, avoid both the movement problems and the weight gain (Chen et al., 2022).

Figure 14.19 PET scans of a patient with schizophrenia

These PET scans of a patient with schizophrenia **(a)** taking clozapine and **(b)** during a period off the drug demonstrate that clozapine increases brain activity in many brain areas. Red indicates the highest activity, followed by yellow, green, and blue.



Hank Morgan/Science Source

An interesting point emerges from studies comparing one antipsychotic drug against another: In 90 percent of the studies that were sponsored by a drug company, the results favored the drug sold by the sponsoring company (Heres et al., 2006). Interesting coincidence, right? It is possible to bias a study in subtle ways, by altering the doses of two drugs, choosing patients who seem likely to respond to the sponsor's drug, or choosing one measurement instead of another to report.

Role of Glutamate

The dopamine hypothesis is incomplete, because about one-third of all patients do not respond well to the drugs that block dopamine, and even when they do, the drugs relieve mainly the positive symptoms with little effect on the negative or cognitive symptoms. Second-generation drugs help somewhat with the negative and cognitive symptoms (Veselinovic et al., 2019). According to the **glutamate hypothesis of schizophrenia,** schizophrenia results at least in part from a dysfunction of glutamate transmission. The original evidence for this hypothesis was that phencyclidine (PCP) and ketamine, which antagonize NMDA-type glutamate receptors, produce effects resembling both the positive and negative symptoms of schizophrenia. They also induce a relapse for someone who has recovered from schizophrenia. (Farber et al., 1999; Hardingham and Do, 2016; Olney and Farber, 1995). Chronic ketamine use causes a loss of gray matter in several brain areas, similar to the pattern sometimes seen in patients with schizophrenia (Chesters et al., 2022).

Researchers do not have a consensus about the role of glutamate, but here is one somewhat complicated version (Egerton et al., 2020): A tendency toward schizophrenia begins with reduced activity of NMDA receptors in the hippocampus, caused by a combination of genetic and environmental forces. Ordinarily, those NMDA receptors stimulate neurons that inhibit other cells from releasing glutamate, but because the NMDA receptors have reduced activity, the result is excessive release of glutamate in other places, contributing to symptoms of the disorder. Excessive glutamate release can overstimulate neurons and thereby kill them and, after prolonged illness, even if someone has recovered from the positive symptoms, many neurons in the cortex may have died, causing negative and cognitive symptoms (Kumar et al., 2020). The increased glutamate can also increase

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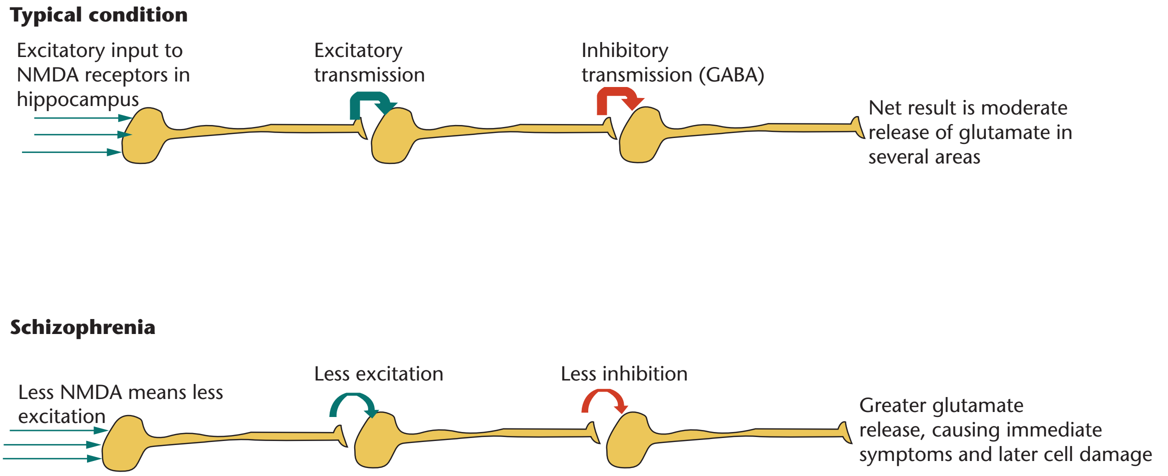
Figure 14.20 The glutamate hypothesis of schizophrenia

Reduced function of NMDA receptors in the hippocampus decreases the inhibition of release of glutamate in the several areas. Excessive glutamate release can damage neurons by overstimulation.


Typical condition
Excitatory input to NMDA receptors in hippocampus
Excitatory transmission
Inhibitory transmission (GABA)
Net result is moderate release of glutamate in several areas
Schizophrenia
Less NMDA means less excitation
Less excitation
Less inhibition
Greater glutamate release, causing immediate symptoms and later cell damage

dopamine release, responsible for the positive symptoms (Lodge and Grace, 2011). Yes, I told you it was going to be complicated. Figure 14.20 attempts to summarize. As a result of the complexity, drugs that affect glutamate release might or might not be helpful, depending on the stage of the disease and other factors.

Stop & Check

29. What are the advantages of the second-generation antipsychotics?
30. How does the glutamate hypothesis explain why negative and cognitive symptoms persist after antipsychotic drugs have relieved the positive symptoms?

See page 490 for the answer.

Module 14.3 | In Closing

Many Remaining Mysteries

In most areas of medicine, treatment today is far more successful than in past decades. However, in psychopathology, and particularly in schizophrenia, research has led to improved understanding without much improvement in patients' outcome (Insel, 2022). One reason is that many patients do not get the treatments that are available, or do not get it early enough. Another is that our understanding of the condition, though improved, is still far from complete.

Research is a little like reading a good mystery novel that presents a mixture of important clues and irrelevant information. In research on schizophrenia, we have much information, but also gaps and points that don't seem to fit. The final chapter of our mystery novel on schizophrenia is incomplete. It will be fascinating to see what develops in future research.

Summary

1. Positive symptoms of schizophrenia (behaviors that are not present in most other people) include hallucinations, delusions, inappropriate emotions, bizarre behaviors, and thought disorder. **482**
2. Negative symptoms (behaviors that are absent) include deficits of social interaction, emotional expression, and speech. **482**

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3. Although cognitive symptoms are not necessary for a diagnosis, most people with schizophrenia have slow processing speed, impairments of memory and attention, and difficulty perceiving other people's emotions and intentions. **482**
4. Before diagnosing someone with schizophrenia, a therapist needs to rule out brain damage, drug abuse, and other conditions that could produce similar symptoms. **482**
5. Although schizophrenia is highly heritable, no common genetic variant produces a large effect. Rare mutations and microdeletions produce larger effects. **483**
6. According to the two-hit hypothesis, many or most cases develop from a combination of genetic or early development problems plus later environmental insults. **484**
7. Many people with schizophrenia show mild abnormalities of brain development, but the brain pattern is highly variable. **485**
8. According to the dopamine hypothesis, schizophrenia is due to excess dopamine activity. Drugs that block dopamine synapses reduce the positive symptoms of schizophrenia, and drugs that increase dopamine activity induce the positive symptoms. **486**
9. Prolonged use of antipsychotic drugs may produce tardive dyskinesia, a movement disorder. Second-generation antipsychotic drugs reduce the risk of tardive dyskinesia. **487**
10. According to the glutamate hypothesis, reduced activity at NMDA synapses in the hippocampus leads to excessive glutamate release, at least in the early stage of the disorder. Prolonged excess glutamate can damage neurons and cause long-lasting negative and cognitive symptoms. **488**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

antipsychotic (neuroleptic) drugs **486**
butyrophenones **486**
chlorpromazine **486**
concordance **483**
delusions **482**
differential diagnosis **482**
DISC1 **484**
dopamine hypothesis of schizophrenia **486**
glutamate hypothesis of schizophrenia **488**
hallucinations **482**
mesolimbocortical system **487**
microdeletion **484**
negative symptoms **482**
neurodevelopmental hypothesis **484**
phenothiazines **486**
positive symptoms **482**
schizophrenia **481**
season-of-birth effect **485**
second-generation antipsychotics **487**
substance-induced psychotic disorder **487**
tardive dyskinesia **487**
two-hit hypothesis **484**

Thought Question

On average, people who use much marijuana are more likely than others to develop schizophrenia. However, over the last several decades, the use of marijuana has increased while the prevalence of schizophrenia has not. What would be a reasonable hypothesis about the relationship between marijuana use and schizophrenia?

Stop & Check Answers

23. Hallucinations are considered a positive symptom because they are present when they should be absent. In this context, "positive" does not mean "good."
24. A biological mother can influence her child's development through prenatal environment as well as genetics.
25. Rare mutations and microdeletions can produce a large effect. Also, genes with small effects can combine with one another or with environmental influences.
26. No common gene or environmental factor by itself has a strong relationship to schizophrenia. A combination of factors seems more likely.
27. Schizophrenia is unlike Parkinson's and Alzheimer's diseases, in which the brain shows progressive deterioration over time.
28. Their ability to relieve schizophrenia correlates strongly with how well they block dopamine synapses.
29. Second-generation antipsychotics are less likely to cause tardive dyskinesia. Also, they alter synapses other than dopamine, in ways that may be helpful.
30. Excessive glutamate release overstimulates neurons and kills some of them, producing negative and cognitive symptoms.

Module 14.3 | End-of-Module Quiz

1. Why is lack of emotional expression considered a "negative" symptom?
   - **a.** It is disadvantageous to the patient.
   - **b.** Only a small percentage of patients have this symptom.
   - **c.** Emotional expressions are absent when they should be present.
   - **d.** Poor emotional expression is caused by decreased activity in certain brain areas.

2. What is the long-term course of schizophrenia?
   - **a.** The symptoms get worse and worse throughout life.
   - **b.** Many people remain steady, some have variable symptoms, and some recover.
   - **c.** Most people suffer through a single episode and then return to normal.
   - **d.** People start with schizophrenia and then switch to bipolar disorder.

3. Which of the following sometimes produces symptoms resembling schizophrenia?
   - **a.** Excessive time on social media
   - **b.** Being cross-eyed and left-handed
   - **c.** Inability to metabolize lactose
   - **d.** Abuse of amphetamine or cocaine

4. Does a single gene ever produce a big increase in risk of schizophrenia?
   - **a.** No.
   - **b.** Yes, one gene causes schizophrenia, but researchers have not found it yet.
   - **c.** Yes, some mutations or microdeletions greatly increase the risk.
   - **d.** Yes, the APOE4 gene greatly increases the risk.

5. According to the two-hit hypothesis, what causes schizophrenia?
   - **a.** A genetic mutation plus a microdeletion
   - **b.** A traumatic experience in childhood and a similar experience later
   - **c.** Damage to both the left hemisphere and the right hemisphere
   - **d.** A genetic predisposition plus an environmental impact

6. Of these, which is the most likely explanation for the season-of-birth effect?
   - **a.** Differences in the age of children when they start school
   - **b.** Temperature at the time of birth
   - **c.** Availability of proteins in the diet
   - **d.** Maternal illness during pregnancy

7. What do first-generation antipsychotic drugs do?
   - **a.** They stimulate oxytocin receptors.
   - **b.** They interfere with reuptake of serotonin and other transmitters.
   - **c.** They block dopamine synapses.
   - **d.** They stimulate GABA synapses.

8. Tardive dyskinesia is a disorder of what?
   - **a.** Social behavior
   - **b.** Memory
   - **c.** Language
   - **d.** Movement

9. According to the glutamate hypothesis, what is the chemical origin of schizophrenia?
   - **a.** Reduced activity at NMDA receptors in the hippocampus
   - **b.** Failure of glutamate neurons to migrate to the prefrontal cortex
   - **c.** Inability to metabolize glutamate
   - **d.** Slower-than-normal action potentials in neurons that release glutamate

Answers: 1c, 2b, 3d, 4c, 5d, 6d, 7c, 8d, 9a.

Module 14.4

Autism Spectrum Disorders

Learning Objectives

After studying this module, you should be able to:

14. Describe the symptoms of autism, noting the variance among individuals.
15. Describe the genetic and environmental contributors.
16. Explain why some children with autism behave more normally when they have a fever.

The term **autism spectrum disorder** recognizes the fact that people vary along a continuum from serious cases to the milder cases that were formerly called *Asperger's syndrome*. Almost anything about autism varies from one person to another. Specialists in the field remark that "if you have seen one child with autism, you have seen one child with autism."

Estimates of the incidence vary, with a median estimate of about 1 in 160 people worldwide, and somewhat more than that in the United States (Elsabbagh et al., 2012). Autism is about four times as common in boys as in girls. When it does occur in females, it tends to be more severe (Turner et al., 2015). It is diagnosed more often today than in the past. Part of the apparent increase is due to greater awareness, but it is also possible that the condition has in fact become more common.

Symptoms and Characteristics

The American Psychiatric Association (2013) lists the following characteristics of autism spectrum disorder:

- Deficits in social and emotional exchange
- Deficits in gestures, facial expressions, and other nonverbal communication
- Stereotyped behaviors, such as repetitive movements (Figure 14.21)
- Resistance to a change in routine
- Either weak or exaggerated responses to stimuli, such as indifference to pain, panicked reaction to a sound, or displeasure at being touched

Figure 14.21 Stereotyped behaviors by an autistic child

Repetitive nonsocial behaviors are common in people with autism.

M. Scott Brauer/Alamy Stock Photo

Most people with autism have additional problems, such as epilepsy, anxiety, poor coordination, or deficits in attention or sleep (Bourgeron, 2015). Abnormalities in the cerebellum are common, associated with clumsiness and impaired voluntary eye movements (Fatemi et al., 2012). Intellect may be impaired, although about two-thirds of people in the autism spectrum have average or above-average intellect (Rosello et al., 2021). Many have excellent specialized skills.

Parents of children with autism often notice a problem from the start, as an infant may not react comfortably to being held. Other problems increase over time. Eye contact with other people gradually declines over the first two years (Jones and Klin, 2013). The problem is not an aversion to eye contact. Once children with autism do make eye contact, they maintain it normally. The problem is that eyes and other social cues do not readily attract their attention (Moriuchi et al., 2016).

Another peculiarity that occurs early is unusual visual exploration of objects. Even as young as age 9 months, many children who will later be diagnosed with autism show prolonged staring at objects, often squinting or blinking, and sometimes glancing at it to the side (Miller et al., 2021).

Genetics and Other Causes

Many cases of autism can be traced to a single gene, but it is not always the same gene. Rare new ("de novo") mutations and copy number duplications can cause autism—in other words, variants that occurred during reproduction, not inherited from a parent (An et al., 2018; Yuen et al., 2017). Some cases relate to mutations that occurred during embryonic development, which therefore show up in some cells and not others (Lim et al., 2017; Sherman et al., 2021). At least one important mutation is to a mitochondrial gene (Aoki and Cortese, 2016). Many cases relate to genetic variants that moderately increase the risk, followed by environmental impacts that magnify the effect. All the genes with strong links to autism affect the early development of the forebrain (Krishnan et al., 2016; Velmeshev et al., 2019; Willsey et al., 2021).

Problems in the prenatal environment can contribute. The risk of autism increases if the mother is exposed during pregnancy to large amounts of pesticides, solvents, perfumes, or air pollutants (He et al., 2022; Mandy and Lai, 2016; Sealey et al., 2016). The risk also increases if the mother has an infection during pregnancy that activates the immune system (Kalish et al., 2021). If the child soon after birth has a gastrointestinal infection, the resulting inflammation can disrupt the blood-brain barrier and predispose to autism (Eshraghi et al., 2021). On the other hand, the risk decreases if the mother gets adequate amounts of **folic acid** (vitamin B_9), vitamin A, and vitamin D during pregnancy (Freedman et al., 2018; Surén et al., 2013). These are important for development of the nervous system.

A large-scale study found that after the birth of a child with autism, a brother or sister born less than 18 months later had a 14.4 percent chance of having autism also, whereas a brother or sister born 4 years later had only a 6.8 percent chance (Risch et al., 2014). The genes are no more similar after a short delay than after a long delay, but the prenatal environments are more similar.

Autism has an increased incidence in families with a history of autoimmune disorders—diseases in which the immune system attacks part of the body (Thom et al., 2019). Some mothers of children with autism have uncommon antibodies that attack certain brain proteins (Marks et al., 2020). Researchers injected pregnant monkeys with antibodies from mothers of children with autism or mothers of unaffected children. Those injected with antibodies from children with autism had more offspring that avoided social contacts (Bauman et al., 2013).

Brain and Sensation

Many brain variations have been reported in people with autism, varying from one individual to another (Frewer et al., 2021). A reasonably consistent pattern is greater than average brain growth in early childhood, causing mean head size to be 10 percent greater than average at age 1 year, followed by greater than average synaptic pruning during early adolescence (Rafiee et al., 2021). By young adulthood, the brain size is close to average, but it took an unusual route to get there (Hahamy et al., 2015; Jumah et al., 2016; Schumann et al., 2010).

Recall that one of the common symptoms of autism is exaggerated responses to stimuli, such as sounds and touches. Lauren Orefice and her associates discovered the reason. Certain genetic mutations that cause autism increase the sensitivity of somatosensory nerves by decreasing inhibitory input to them (Orefice et al., 2019). An infant who finds touch stimuli unpleasant will avoid cuddling with parents, therefore becoming less prone to develop a close social relationship. Overreactivity of sensory neurons correlates strongly with impaired social behavior and communication (Orefice, 2020).

At about the time when Orefice made that discovery, another laboratory demonstrated that having a fever causes the immune system to release chemicals including *interleukin 17a* that suppress activity in the primary somatosensory cortex (Reed et al., 2020). That finding is theoretically important for a curious reason: For decades, many parents had reported that when their autistic children had a fever, they behaved more like typical children (Sullivan, 1980). Theorists mostly ignored these reports, because they had no hypothesis to explain them. Now we understand: The children ordinarily have excessive responses to sensory stimuli, causing excessive responses in the somatosensory cortex. A fever restores normality, analogous to turning down the volume on a painfully loud device.

Lauren Orefice

Lauren Orefice

Genetics and early life experiences influence how we feel the world around us through our sense of touch. Our unique tactile sensitivities contribute to how our brains develop and how we interact socially, ultimately shaping who we are as individuals. (Personal communication)

Stop & Check

31. Having a sibling with autism who is close to your age increases your own risk more than having a sibling with autism who is much older or younger. What conclusion does this observation imply?
32. Why do many children with autism overreact to sensory stimuli, and how does that reaction relate to social behavior?

See page 495 for the answer.

Treatments

So far, no medical intervention provides significant help for the core symptoms of autism, although many researchers hope that increased understanding will lead to new possibilities. Behavioral treatments address the deficits in social behavior and communication. Parents, teachers, and therapists focus on eliciting the child's attention and reinforcing favorable behaviors. This procedure is successful with many children but not all. Cognitive behavioral therapy provides moderate benefits according to therapists and parents, but not according to the people with autism themselves (Weston et al., 2016).

Parents who grow understandably disappointed with these treatments are vulnerable to anyone who promises something better. A huge number of fad treatments have arisen, including special diets, chelation, music, and therapeutic touch. A treatment can become popular despite a lack of evidence to support it, or even the presence of evidence that it is harmful. Many fad treatments make the parents feel good that they are trying something, without actually accomplishing any benefits (Matson et al., 2013).

Module 14.4 | In Closing

A Complex Disorder

I have to apologize for ending this book on such a discouraging note: You have just read that researchers have increased our understanding of the causes of autism, but so far we have no effective treatment. Alas. Still, remember those words "so far." Many problems that once seemed intractable became more solvable after further research. Biological psychology is a work in progress. We are constantly learning more, and yet much remains to be learned. I hope that some of the readers of this book will go on to make research contributions of their own.

Summary

1. Primary symptoms of autism spectrum disorder include a deficiency of social behavior and communication, repetitive stereotyped behaviors, resistance to change, and either reduced or exaggerated responses to sensory stimuli. **492**
2. Rare de novo genetic mutations cause some cases of autism. Other cases reflect the combined effects of a risk gene and an environmental insult. **493**
3. Difficulties in the prenatal environment, including autoimmune disorders, lead to some cases of autism. Consuming certain vitamins during pregnancy decreases the probability of an autistic child. **493**
4. A common pattern is for brain size to increase faster-than-normal during infancy, and then to have increased synaptic pruning in early adolescence. **493**
5. Sensory nerves produce stronger than average responses in the cortex, because of reduced inhibition. Because a fever reduces activity in the somatosensory cortex, some children with autism behave more normally when they have a fever. **493**

Key Terms

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary at the end of this book.

autism spectrum disorder	**492**
folic acid	**493**

Thought Question

Some people have their chromosomes examined to check for predispositions to various illnesses, such as breast cancer. What would be the pros and cons of checking for genes associated with psychological disorders?

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Stop & Check Answers

31. Genetics cannot be the whole explanation for autism. Factors in the prenatal environment may contribute. The prenatal environment is more similar for siblings close in age.

32. Certain mutations that cause autism decrease the inhibition to sensory nerves, causing more intense stimulation. Children experiencing intense reactions to touch will avoid physical contact with others.

Module 14.4 | End-of-Module Quiz

1. The clumsiness and impaired voluntary eye movements of many children with autism implies decreased activity of what brain area?

a. Corpus callosum
b. Medulla
c. Cerebellum
d. Amygdala

2. What is meant by a "de novo" mutation?

a. One that is not inherited from the parents
b. One that produces a major deficit
c. One that alters early development of the brain
d. One that is intermediate between dominant and recessive

3. In what way does the "two-hit" hypothesis apply to autism as well as schizophrenia?

a. The condition results from a loss of both excitatory and inhibitory transmission.
b. Both the brain and the digestive system are abnormal.
c. The child must inherit genetic mutations from both the mother and the father.
d. Many cases result from both genetic and environmental influences.

4. What dietary supplement during pregnancy decreases the probability of having a child with autism?

a. Calcium
b. Vitamin C
c. Fish oil
d. Folic acid

5. Which of the following is common for children with autism, at age 1 year?

a. The brain's norepinephrine concentration is higher than average.
b. The axons conduct impulses faster than average.
c. The brain is larger than average.
d. The cerebral ventricles are larger than average.

6. Why do some children with autism behave more normally when they have a fever?

a. Fever increases activity in the occipital cortex.
b. Fever decreases appetite.
c. Fever increases sleep.
d. Fever decreases activity in the somatosensory cortex.

Answers: 1c, 2a, 3d, 4d, 5c, 6d.

Suggestion for Further Reading

Insel, T. (2022). *Healing*. (Penguin). A thoughtful and insightful discussion of mental disorders by the former Director of the National Institute of Mental Health.

Brief, Basic Chemistry

Appendix A

Main Ideas

1. All matter is composed of a limited number of elements that combine in endless ways.
2. Atoms, the component parts of an element, consist of protons, neutrons, and electrons. Most atoms can gain or lose electrons, or share them with other atoms.
3. The chemistry of life is predominantly the chemistry of carbon compounds.

Introduction

To understand certain aspects of biological psychology, particularly the action potential and the molecular mechanisms of synaptic transmission, you need to know a little about chemistry. If you have taken a high school or college course and remember the material reasonably well, you should have no trouble with the chemistry in this text. If your knowledge of chemistry is pretty hazy, this appendix will help. (If you plan to take other courses in biological psychology, you should study as much biology and chemistry as possible.)

Elements and Compounds

If you look around, you will see an enormous variety of materials—dirt, water, wood, plastic, metal, cloth, glass, your own body. Every object is composed of a small number of basic building blocks. If a piece of wood catches fire, it breaks down into ashes, gases, and water vapor. The same is true of your body. An investigator could take those ashes, gases, and water, and break them down by chemical and electrical means into carbon, oxygen, hydrogen, nitrogen, and a few other materials. Eventually, however, the investigator arrives at a set of materials that cannot be broken down further: Pure carbon or pure oxygen, for example, cannot be converted into anything simpler, at least not by ordinary chemical means. (High-power bombardment with subatomic particles is another story.) The matter we see is composed of **elements** (materials that cannot be broken down into other materials) and **compounds** (materials made up by combining elements).

Chemists have found 92 elements in nature, and they have constructed more in the laboratory. (Actually, one of the 92—technetium—is so rare as to be virtually unknown in nature.) Figure A.1, the periodic table, lists each of these elements. Of these, only a few are important for life on Earth. Table A.1 shows the elements commonly found in the human body.

Note that each element has a one- or two-letter abbreviation, such as O for oxygen, H for hydrogen, and Ca for calcium. These are internationally accepted symbols that facilitate communication among chemists who speak different languages. For example, element number 19 is called potassium in English, potassio in Italian, kālijs in Latvian, and draslík in Czech. But chemists in all countries use the symbol K (from *kalium,* the Latin word for "potassium"). Similarly, the symbol for sodium

Table A.1 | The Elements That Compose Almost All of the Human Body

Element	Symbol	Percentage by Weight in Human Body
Oxygen	O	65
Carbon	C	18
Hydrogen	H	10
Nitrogen	N	3
Calcium	Ca	2
Phosphorus	P	1.1
Potassium	K	0.35
Sulfur	S	0.25
Sodium	Na	0.15
Chlorine	CI	0.15
Magnesium	Mg	0.05
Iron	Fe	Trace
Copper	Cu	Trace
Iodine	I	Trace
Fluorine	F	Trace
Manganese	Mn	Trace
Zinc	Zn	Trace
Selenium	Se	Trace
Molybdenum	Mo	Trace

Figure A.1 The periodic table of chemistry

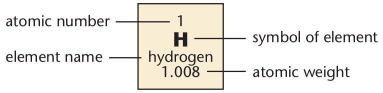
Periodic Table of the Elements

Period	Alkali Metals	Alkaline Earth Metals	Transition Elements														Halogens	Noble Gases
	1 IA	2 IIA	3 IIIB	4 IVB	5 VB	6 VIB	7 VIIB	8 VIIIB	9 VIIIB	10 VIIIB	11 IB	12 IIB	13 IIIA	14 IVA	15 VA	16 VIA	17 VIIA	18 VIIA
1	1 **H** hydrogen 1.008																	2 **He** helium 4.003
2	3 **Li** lithium 6.941	4 **Be** beryllium 9.012											5 **B** boron 10.81	6 **C** carbon 12.011	7 **N** nitrogen 14.007	8 **O** oxygen 16.0	9 **F** fluorine 18.999	10 **Ne** neon 20.179
3	11 **Na** sodium 22.99	12 **Mg** magnesium 24.305											13 **Al** aluminum 26.982	14 **Si** silicon 28.085	15 **P** phosphorous 30.974	16 **S** sulfur 32.060	17 **Cl** chlorine 35.453	18 **Ar** argon 39.948
4	19 **K** potassium 39.098	20 **Ca** calcium 40.08	21 **Sc** scandium 44.955	22 **Ti** titanium 47.90	23 **V** vanadium 50.941	24 **Cr** chromium 51.996	25 **Mn** manganese 54.938	26 **Fe** iron 55.847	27 **Co** cobalt 58.933	28 **Ni** nickel 58.70	29 **Cu** copper 63.546	30 **Zn** zinc 65.38	31 **Ga** gallium 69.72	32 **Ge** germanium 72.59	33 **As** arsenic 74.922	34 **Se** selenium 78.96	35 **Br** bromine 79.904	36 **Kr** krypton 83.80
5	37 **Rb** rubidium 85.468	38 **Sr** strontium 87.62	39 **Y** yttrium 88.906	40 **Zr** zirconium 91.22	41 **Nb** niobium 92.906	42 **Mo** molybdenum 95.940	43 **Tc** technetium (97)	44 **Ru** ruthenium 101.07	45 **Rh** rhodium 102.905	46 **Pd** palladium 106.40	47 **Ag** silver 107.868	48 **Cd** cadmium 112.41	49 **In** indium 114.82	50 **Sn** tin 118.69	51 **Sb** antimony 121.75	52 **Te** tellurium 127.60	53 **I** iodine 126.904	54 **Xe** xenon 131.30
6	55 **Cs** cesium 132.905	56 **Ba** barium 137.33	57 **La** lanthanum 138.906 †	72 **Hf** hafnium 178.49	73 **Ta** tantalum 180.948	74 **W** tungsten 183.85	75 **Re** rhenium 186.207	76 **Os** osmium 190.20	77 **Ir** iridium 192.22	78 **Pt** platinum 195.09	79 **Au** gold 196.967	80 **Hg** mercury 200.59	81 **Tl** thallium 204.37	82 **Pb** lead 207.20	83 **Bi** bismuth 208.980	84 **Po** polonium (209)	85 **At** astatine (210)	86 **Rn** radon (222)
7	87 **Fr** francium (223)	88 **Ra** radium 226.025	89 **Ac** actinium (227) ‡	104 **Rf** rutherfordium (261)	105 **Db** dubnium (262)	106 **Sg** seaborgium (266)	107 **Bh** bohrium (264)	108 **Hs** hassium (269)	109 **Mt** meitnerium (268)	110 **Ds** darmstadtium (271)	111 **Rg** roentgenium (272)	112 **Cn** copernicium (285)	113 **Nh** Nihonium (286)	114 **Uuq** ununquadium (289)	115 **Mc** Moscovium (289)	116 **Uuh** ununhexium (292)	117 **Ts** Tennessine (294)	118 **Og** Oganesson (294)

Inner Transition Elements

† Lanthanides 6	58 **Ce** cerium 140.12	59 **Pr** praseodymium 140.908	60 **Nd** neodymium 144.24	61 **Pm** prometheum (145)	62 **Sm** samarium 150.40	63 **Eu** europium 151.96	64 **Gd** gadolinium 157.25	65 **Tb** terbium 158.925	66 **Dy** dysprosium 162.50	67 **Ho** holmium 164.93	68 **Er** erbium 167.26	69 **Tm** thulium 168.934	70 **Yb** ytterbium 173.04	71 **Lu** lutetium 174.97
‡ Actinides 7	90 **Th** thorium 232.038	91 **Pa** protactinium 231.036	92 **U** uranium 238.029	93 **Np** neptunium (237)	94 **Pu** plutonium (244)	95 **Am** americium (243)	96 **Cm** curium (247)	97 **Bk** berkelium (247)	98 **Cf** californium (251)	99 **Es** einsteinium (254)	100 **Fm** fermium (257)	101 **Md** mendelevium (258)	102 **No** nobelium (255)	103 **Lr** lawrencium (260)

Key



It is called "periodic" because certain properties show up at periodic intervals. For example, the column from lithium down consists of metals that readily form salts. The column at the far right consists of gases that do not readily form compounds. Elements 114 and 116 have only tentative names and symbols.

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is Na (from *natrium*, the Latin word for “sodium”), and the symbol for iron is Fe (from the Latin word *ferrum*).

A compound is represented by the symbols for the elements that compose it. For example, NaCl stands for sodium chloride (common table salt). H_2O, the symbol for water, indicates that water consists of two parts of hydrogen and one part of oxygen.

Atoms and Molecules

A block of iron can be chopped finer and finer until it is divided into tiny pieces that cannot be broken down any further. These pieces are called **atoms**. Every element is composed of atoms. A compound, such as water, can also be divided into tinier and tinier pieces. The smallest possible piece of a compound is called a **molecule**. A molecule of water can be further decomposed into two atoms of hydrogen and one atom of oxygen, but when that happens the compound is broken and is no longer water. A molecule is the smallest piece of a compound that retains the properties of the compound.

An atom is composed of subatomic particles, including protons, neutrons, and electrons. A proton has a positive electrical charge, a neutron has a neutral charge, and an electron has a negative charge. The nucleus of an atom—its center—contains one or more protons plus a number of neutrons. Electrons are found in the space around the nucleus. Because an atom has the same number of protons as electrons, the electrical charges balance out. (Ions, which we will soon consider, have an imbalance of positive and negative charges.)

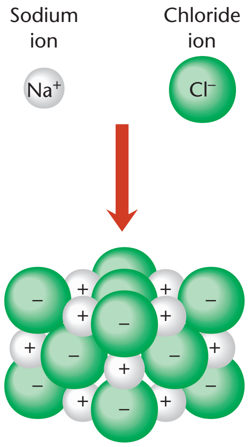
The difference between one element and another is in the number of protons in the nucleus of the atom. Hydrogen has just one proton, for example, and oxygen has eight. The number of protons is the **atomic number** of the element; in the periodic table it is recorded at the top of the square for each element. The number at the bottom is the element’s **atomic weight**, which indicates the weight of an atom relative to the weight of one proton. A proton has a weight of one unit, a neutron has a weight just trivially greater than one, and an electron has a weight just trivially greater than zero. The atomic weight of the element is the number of protons in the atom plus the average number of neutrons. For example, most hydrogen atoms have one proton and no neutrons; a few atoms per thousand have one or two neutrons, giving an average atomic weight of 1.008. Sodium ions have 11 protons; most also have 12 neutrons, and the atomic weight is slightly less than 23. (Can you figure out the number of neutrons in the average potassium atom? Refer to Figure A.1.)

Ions and Chemical Bonds

An atom that has gained or lost one or more electrons is called an **ion**. For example, if sodium and chloride come together, the sodium atoms readily lose one electron each and the chloride atoms gain one each. The result is a set of positively charged sodium ions (indicated Na^+) and negatively charged chloride ions (Cl^-). Potassium atoms, like sodium atoms, tend to lose an electron and to become positively charged ions (K^+); calcium ions tend to lose two electrons and gain a double positive charge (Ca^{++}).

Figure A.2 The crystal structure of sodium

Each sodium ion is surrounded by chloride ions, and each chloride ion is surrounded by sodium ions; no ion is bound to any other single ion in particular.



Part of a sodium crystal

Because positive charges attract negative charges, sodium ions attract chloride ions. When dry, sodium and chloride form a crystal structure, as Figure A.2 shows. (In water solution, the two kinds of ions move about haphazardly, occasionally attracting one another but then pulling apart.) The attraction of positive ions for negative ions forms an **ionic bond**. In other cases, instead of transferring an electron from one atom to another, some pairs of atoms share electrons with each other, forming a **covalent bond**. For example, two hydrogen atoms bind, as shown in Figure A.3, and two hydrogen atoms bind with an oxygen atom, as shown in Figure A.4. Atoms that are attached by a covalent bond cannot move independently of one another.

Figure A.3 Structure of a hydrogen molecule

A hydrogen atom has one electron; in the compound the two atoms share the two electrons equally.

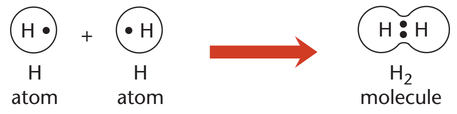


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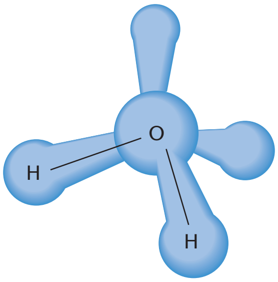
Figure A.4 Structure of a water molecule

The oxygen atom shares a pair of electrons with each hydrogen atom. Oxygen holds the electrons more tightly, making the oxygen part of the molecule more negatively charged than the hydrogen part of the molecule.



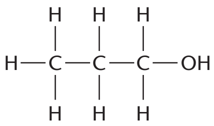
Reactions of Carbon Atoms

Living organisms depend on the enormously versatile compounds of carbon. Because of the importance of these compounds for life, the chemistry of carbon is known as organic chemistry.

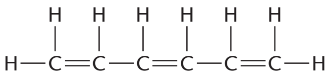
Carbon atoms form covalent bonds with hydrogen, oxygen, and a number of other elements. They also form covalent bonds with other carbon atoms. Two carbon atoms may share from one to three pairs of electrons. Such bonds can be indicated as follows:

C−C	Two atoms share one pair of electrons.
C=C	Two atoms share two pairs of electrons.
C≡C	Two atoms share three pairs of electrons.

Each carbon atom ordinarily forms four covalent bonds, either with other carbon atoms, with hydrogen atoms, or with other atoms. Many biologically important compounds include long chains of carbon compounds linked to one another, such as:

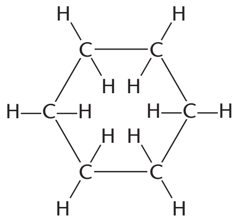


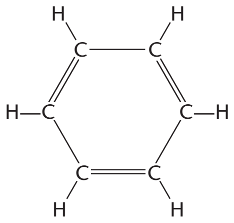
$$\begin{array}{ccccccc} & H & & H & & H & \\ & | & & | & & | & \\ H- & C & - & C & - & C & -OH \\ & | & & | & & | & \\ & H & & H & & H & \end{array}$$



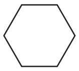
$$\begin{array}{ccccccccccccc} & H & & H & & H & & H & & H & & H & \\ & | & & | & & | & & | & & | & & | & \\ H- & C & = & C & - & C & = & C & - & C & = & C & -H \end{array}$$

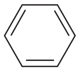
Note that each carbon atom has a total of four bonds, counting each double bond as two. In some molecules, the carbon chain loops around to form a ring:



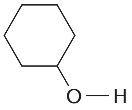


Ringed structures are common in organic chemistry. To simplify the diagrams, chemists often omit the hydrogen atoms. You can simply assume that each carbon atom in the diagram has four covalent bonds and that all the bonds not shown are with hydrogen atoms. To further simplify the diagrams, chemists often omit the carbon atoms themselves, showing only the carbon-to-carbon bonds. For example, the two molecules shown in the previous diagram might be rendered as follows:





If a particular carbon atom has a bond with some atom other than hydrogen, the diagram shows the exception. For example, in each of the two molecules diagrammed below, one carbon has a bond with an oxygen atom, which in turn has a bond with a hydrogen atom. All the bonds that are not shown are carbon–hydrogen bonds.



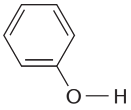


Figure A.5 illustrates some carbon compounds that are critical for animal life. Purines and pyrimidines form the central structure of DNA and RNA, the chemicals responsible for heredity. Proteins, fats, and carbohydrates are the primary types of fuel that the body uses. Figure A.6 displays the chemical structures of seven neurotransmitters that are extensively discussed in this text.

Chemical Reactions in the Body

A living organism is an immensely complicated, coordinated set of chemical reactions. Life requires that the rate of each reaction be carefully regulated. In many cases one reaction produces a chemical that enters into another reaction, which produces another chemical that enters into another reaction, and so forth. If any one of those reactions is too rapid compared to the others, the chemical it produces will accumulate to possibly harmful levels. If a reaction is too slow, it will not produce enough product and the next reaction will be stalled.

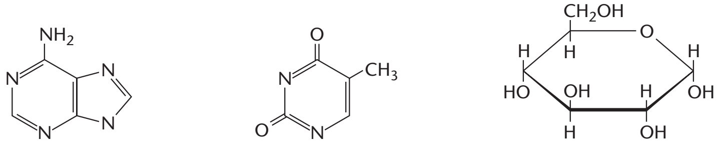
Enzymes are proteins that control the rate of chemical reactions. Each reaction is controlled by a particular enzyme. Enzymes are a type of catalyst. A catalyst is any chemical that facilitates a reaction among other chemicals without being altered itself in the process.

The Role of ATP

The body relies on **ATP (adenosine triphosphate)** as its main way of sending energy where it is needed (see Figure A.7). Much of the energy derived from food goes into forming ATP molecules that eventually provide energy for the muscles and other body parts.

Figure A.5 Structures of some important biological molecules

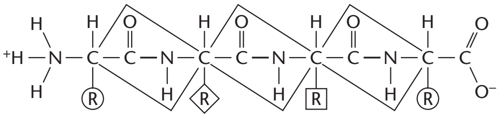
The R in the protein represents a point of attachment for various chains that differ from one amino acid to another. Actual proteins are much longer than the chemical shown here.


NH$_2$
N
N
N
N
O
N
CH$_3$
O
N
CH$_2$OH
O
H
H
H
HO
OH
H
OH
H
OH

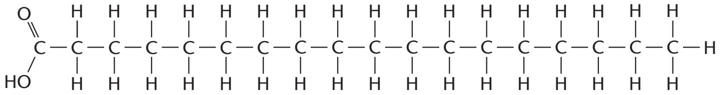
Adenine
(a purine)

Thymine
(a pyrimidine)

Glucose
(a carbohydrate)

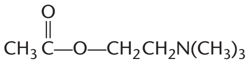

H
H
O
H
O
H
O
H
O
$^+$H
N
C
C
N
C
C
N
C
C
N
C
C
H
R
H
R
H
R
H
R
O$^-$

(a protein)


O
C
HO
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
H

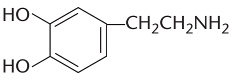
Stearic acid
(a fat)

Figure A.6 Chemical structures of seven abundant neurotransmitters

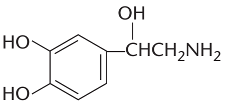


$CH_3\overset{\overset{O}{\|}}{C}-O-CH_2CH_2N(CH_3)_3$

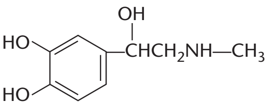
Acetylcholine


HO
HO
CH$_2$CH$_2$NH$_2$

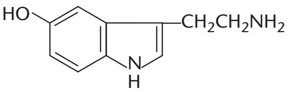
Dopamine


OH
HO
CHCH$_2$NH$_2$
HO

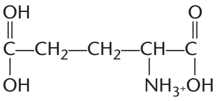
Norepinephrine


OH
HO
CHCH$_2$NH—CH$_3$
HO

Epinephrine

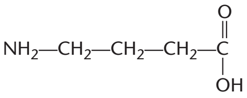

HO
CH$_2$CH$_2$NH$_2$
N
H

Serotonin
(5-hydroxytryptamine)



$\underset{\overset{|}{OH}}{\overset{\overset{OH}{\|}}{C}}-CH_2-CH_2-\underset{\overset{|}{NH_3^+}}{CH}-\underset{\overset{|}{OH}}{\overset{\overset{O}{\|}}{C}}$

Glutamate

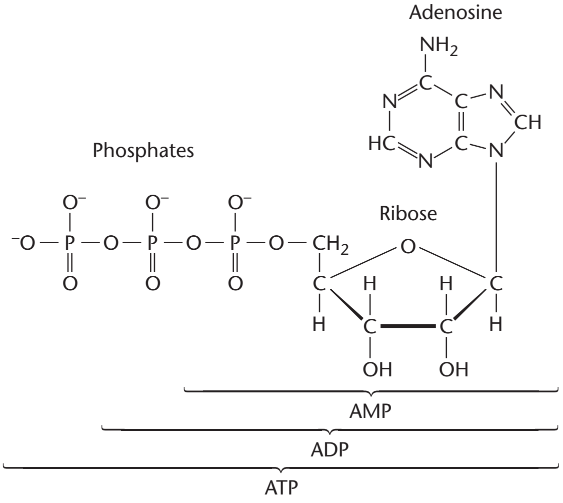


$NH_2-CH_2-CH_2-CH_2-\underset{\overset{|}{OH}}{\overset{\overset{O}{\|}}{C}}$

GABA (γ-amino-butyric acid)

Figure A.7 ATP, composed of adenosine, ribose, and three phosphates

ATP can lose one phosphate group to form ADP (adenosine diphosphate) and then lose another one to form AMP (adenosine monophosphate). Each time it breaks off a phosphate group, it releases energy.


Adenosine
NH$_2$
N
C
C
N
CH
HC
N
C
N
Phosphates
O$^-$
O$^-$
O$^-$
$^-$O
P
O
P
O
P
O
CH$_2$
O
O
O
Ribose
O
C
H
H
C
H
C
C
H
OH
OH
H
AMP
ADP
ATP

ATP consists of adenosine bound to ribose and three phosphate groups (PO_3). Phosphates form high-energy covalent bonds. That is, a large amount of energy is required to form the bonds, and a large amount of energy is released when they break. ATP can break off one or two of its three phosphates to provide energy.

Summary

1. Matter is composed of 92 elements that combine to form an endless variety of compounds. **496**
2. An atom is the smallest piece of an element. A molecule is the smallest piece of a compound that maintains the properties of the compound. **498**
3. The atoms of some elements can gain or lose an electron, thus becoming ions. Positively charged ions attract negatively charged ions, forming an ionic bond. In some cases two or more atoms may share electrons, thus forming a covalent bond. **498**
4. The principal carrier of energy in the body is a chemical called ATP. **499**

Key Terms

atom	**498**
atomic number	**498**
atomic weight	**498**
ATP (adenosine triphosphate)	**499**
compound	**496**
covalent bond	**498**
element	**496**
enzyme	**499**
ion	**498**
ionic bond	**498**
molecule	**498**

Society for Neuroscience Policies on the Use of Animals and Human Subjects in Research

Appendix B

Introduction

The Society for Neuroscience, as a professional society for basic and clinical researchers in neuroscience, endorses and supports the appropriate and responsible use of animals as experimental subjects. Knowledge generated by neuroscience research on animals has led to important advances in the understanding of diseases and disorders that affect the nervous system and in the development of better treatments that reduce suffering in humans and animals. This knowledge also makes a critical contribution to our understanding of ourselves, the complexities of our brains and what makes us human. Continued progress in understanding how the brain works and further advances in treating and curing disorders of the nervous system require investigation of complex functions at all levels in the living nervous system. Because no adequate alternatives exist, much of this research must be done on animal subjects. The Society takes the position that neuroscientists have an obligation to contribute to this progress through responsible and humane research on animals.

Several functions of the Society are related to the use of animals in research. A number of these involve decisions about research conducted by members of the Society, including the scheduling of scientific presentations at the Annual Meeting, the review and publication of original research papers in *The Journal of Neuroscience* and the defense of members whose ethical use of animals in research is questioned by animal rights activists. The Society's support for the research of individual members defines a relationship between the Society and its members. The purpose of this document is to outline the policy that guides that relationship. Compliance with the following policy will be an important factor in determining the suitability of research for presentation at the Annual Meeting or for publication in *The Journal of Neuroscience* and in situations where the Society is asked to provide public and active support for a member whose use of animals in research has been questioned.

The responsibility for implementing the policy in each of these areas rests with the relevant administrative body (Program Committee, Publications Committee, Editorial Board and Committee on Animals in Research, respectively) in consultation with Council.

Policy on the Use of Animals in Neuroscience Research

Neuroscience research uses complicated, often invasive methods, each of which is associated with different problems, risks, and specific technical considerations. An experimental method that would be deemed inappropriate for one kind of research may be the method of choice for another kind of research. It is therefore impossible for the Society to define specific policies and procedures for the care and use of all research animals and for the design and conduct of every neuroscience experiment.

The U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) and the *Guide for the Care and Use of Laboratory Animals* (the Guide) describe general policies and procedures designed to ensure the humane and appropriate use of live vertebrate animals in all forms of biomedical research. The Society finds the policies and procedures set forth in the PHS Policy and the Guide to be both necessary and sufficient to ensure a high standard of animal care and use and adopts them as its official Policy on the Use of Animals in Neuroscience Research (Society Policy). All Society members are expected to conduct their animal research in compliance with this policy. Members are required to verify that they have done so when submitting abstracts for presentation at the Annual Meeting or manuscripts for publication in *The Journal of Neuroscience.* Adherence to the Society policy is also an important step toward receiving help from the Society in responding to questions about a member's use of animals in research. A complete description of what to do if your research is questioned is included in this handbook. Also, a complete description of SfN's policy and procedures for defending members whose research comes under attack can be obtained by contacting the Society's Central Office.

Local Committee Review

An important element of the Society Policy is the establishment of a local committee that is charged with reviewing and approving all proposed animal care and use procedures. In addition to scientists experienced in research involving animals and a veterinarian, the membership of this local committee should include a person who is not affiliated with the member's institution in any other way. In reviewing a proposed use of animals, the committee should evaluate the adequacy of institutional policies, animal husbandry, veterinary care, and the physical plant. The committee should pay specific attention to proposed procedures for animal procurement, quarantine and stabilization, separation by species, disease diagnosis and treatment, anesthesia and analgesia, surgery and postsurgical care, and euthanasia. The review committee also should ensure that procedures involving live vertebrate animals are designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge or the good of society. This review and approval of a member's use of live vertebrate animals in research by a local committee is an essential component of the Society Policy. For assistance in developing appropriate animal care and use procedures and establishing a local review committee, call the Society and consult the documents recommended at the end of this section.

Other Laws, Regulations, and Policies

In addition to complying with the policy described above, Society members who reside in North America must also adhere to all relevant national, state, or local laws and/or regulations that govern their use of animals in neuroscience research. Thus, U.S. members must observe the U.S. Animal Welfare Act (as amended in 1985) and its implementing regulations from the U.S. Department of Agriculture. Canadian members must abide by the January 1993 Guide to the Care and Use of Experimental Animals. Members in Mexico must comply with the "Seventh Title of the Regulations of the General Law of Health Regarding Health Research." In addition to complying with the laws and regulations of their home countries, foreign members of the Society should adhere to the official Society Policy outlined here.

Recommended References

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General Principles

The following principles, based largely on the PHS Policy on Humane Care and Use of Laboratory Animals, can be a useful guide to designing and implementing experimental procedures involving laboratory animals.

Animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results.

Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain, is imperative.

Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

Postoperative care of animals should minimize discomfort and pain and, in any case, should be equivalent to accepted practices in schools of veterinary medicine.

Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure. If the study requires the death of the animal, the animal must be killed in a humane manner.

Living conditions should be appropriate for the species and contribute to the animals' well-being. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, appropriate veterinary care shall be provided.

Exceptions to these principles require careful consideration and should only be made by an appropriate review group such as an institutional animal care and use committee.

Policy on the Use of Human Subjects in Neuroscience Research

Experimental procedures involving human subjects must have been conducted in conformance with the policies and principles contained in the Federal Policy for the Protection of Human Subjects (U. S. Office of Science and Technology Policy) and in the Declaration of Helsinki. When publishing a paper in *The Journal of Neuroscience* or submitting an abstract for presentation at the Annual Meeting, authors must sign a statement of compliance with this policy.

Recommended References

"Declaration of Helsinki." Adopted by 18th World Medical Assembly, Helsinki, 1964; revised by 29th World Medical Assembly, Tokyo, 1975; Venice, 1983; and Hong Kong, 1989.

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Antabuse drug that antagonizes the effects of acetaldehyde dehydrogenase by binding to its copper ion, 467
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- **Antagonistic muscles** opposing sets of muscles that are required to move a leg or arm back and forth, *43*, 226, *227*
- Anterior, *67*, *68*, 74
- **Anterior commissure** bundle of axons that connects the two hemispheres of the cerebral cortex, *75*, 81, 363, 424, *428*
- **Anterior pituitary** portion of the pituitary gland, composed of glandular tissue, 58, *58*, *61*, *294*
- **Anterograde amnesia** inability to form memories for events that happened after brain damage, 395
- **Antibodies** Y-shaped proteins that attach to particular kinds of antigens, 377, *378*
- Antidepressant drugs, 472–477
  - alternatives to, 475–477
  - and dopamine, 472–473, *473*
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- **Antidiuretic hormone (ADH)** hormone that enables the kidneys to reabsorb water from urine; also known as vasopressin, 300
- **Antigens** surface proteins on a cell that identify the cell as your own, 377, *378*
- Antihistamine drugs, 207, 274
- **Antipsychotic drugs** drugs that tend to relieve schizophrenia and similar conditions, 486–487
- **Antisaccade task** a voluntary eye movement away from the normal direction, 237
- Antisocial behavior, 364, *364*. *See also* Aggressive behaviors
- Anxiety alcohol and, 374
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- **Aphasia** language impairment, 434–436, *436*
- *Aplysia*, *409*, 409–410, *410*
- **Apoptosis** a programmed mechanism of cell death, 122, 124
- **Arcuate nucleus** hypothalamic area with sets of neurons for hunger and satiety, 311–312, *330*
- **Area A1.** *See* **Primary auditory cortex**
- **Area V1.** *See* **Primary visual cortex**
- **Area V2.** *See* **Secondary visual cortex**
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- **Artificial selection** a process of selecting plants/animals for desired traits, 110
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- **Associativity** property that pairing a weak input with a stronger input enhances its later response, 411, *411*
- **Astigmatism** a decreased responsiveness to one kind of line or another, caused by an asymmetric curvature of the eyes, 171, *171*
- **Astrocytes** star-shaped glia that synchronize the activity of the axons, 18, *20*, 138
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- ATP (adenosine triphosphate), *50*
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- **Atypical antidepressants** drugs with antidepressant effects that do not fit into any of the other antidepressant categories, 473
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- Auditory cortex, 191–193, *192*–193
- **Autism spectrum disorders** family of psychological disorders marked by impaired social and emotional exchange and other symptoms, 492–494
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  - symptoms, 492, *492*
  - treatments, 494
- **Autonomic nervous system** part of the peripheral nervous system that controls the heart, intestines, and other organs, 67, *67*, 69–70
- **Autoreceptor** receptor on a presynaptic neuron that responds to the released transmitter by inhibiting further release of it, 55
- **Autoreceptors** receptors on a presynaptic neuron that provide negative feedback by responding to the transmitter released by that neuron, 55
- **Autosomal genes** all chromosomes other than X and Y, 106
- **Axon** thin fiber of constant diameter; the neuron's information sender, 16–17, *17*
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  - and muscle fibers, 226–230
  - pathfinding by, *120*, 120–122
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- *Bacopa monnieri,* 414
- **Ballistic movement** motion that proceeds as a single organized unit that cannot be redirected once it begins, 230
- **BAS.** *See* **Behavioral activation system**
- **Basal forebrain** area anterior and dorsal to the hypothalamus; includes cell clusters that promote wakefulness and sleep, 75, *77*, *273*, 274
- **Basal ganglia** a group of subcortical forebrain structures lateral to the thalamus, 75, *76*, 242–244, *488*
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  - and movement, 242–244, *243*
  - overview of, 75, 242–244
- **Basal metabolism** energy used to maintain a constant body temperature while at rest, 294–295
- Basilar membrane, 189–191, *190*, 191
- Bats, 187
- Battle fatigue. *See* **Post-traumatic stress disorder (PTSD)**
- B cells, 377, *378*
- **BDNF.** *See* **Brain-derived neurotrophic factor**
- **Bed nucleus of the stria terminalis** a set of neurons that connect to the amygdala, 368, *368*
- **Behavioral activation system (BAS)** left brain hemispheric activity marked by low to moderate autonomic arousal and a tendency to approach, which could characterize either happiness or anger, 356
- Behavioral development, and brain development, 131–132
- **Behavioral inhibition system (BIS)** right brain hemispheric activity, which increases attention and arousal, inhibits action, and stimulates emotions such as fear and disgust, 356
- **Behavioral medicine** field that includes the effects of diet, smoking, exercise, stressful experiences, and other behaviors on health, 376
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- **Benzodiazepines** a class of anti-anxiety drugs, 372, *373*
- Bilingual people, 436
- **Binding problem** question of how various brain areas produce a perception of a single object, 87–88, *88*
- **Binocular rivalry** alternating conscious perceptions that occur when one views incompatible displays with the two eyes, *444*, 444–445, *445*
- Biological clock, 263–266
- **Biological psychology** the study of the physiological, evolutionary, and

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Bipolar disorder a condition that alternates between depression and mania, *477*, 477–478
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Butyrophenones a chemical family that includes antipsychotic drugs (haloperidol) that relieve the positive symptoms of schizophrenia, 486

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Cannabinoids chemicals related to Δ-9-THC, 55, *56*, 137, *137*, 206
Capsaicin a chemical, found in hot peppers, that produces a painful burning sensation, 200, 207
Cardiac muscles muscles of the heart that have properties intermediate between those of smooth and skeletal muscles, 226, *227*
Catecholamines compounds that contain a catechol and an amine group, 50
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Complex cell type of visual cortex cell located in areas V1 and V2 that responds to a pattern of light in a particular orientation anywhere within its large receptive field, 166, *167*, *168*
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Conditioned stimulus (CS) stimulus that evokes a particular response only after it has been paired with an unconditioned stimulus, 384, *385*
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Cones type of retinal receptor that contributes to color perception, *152*, 152–153, *155*, *161*
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Flexor muscle that flexes the limb, 226, *227*
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FMRI. *See* **Functional magnetic resonance imaging**
Focal hand dystonia (musician's cramp) a disorder where one or more fingers is in constant contraction or where moving one finger independently of others is difficult, 130
Folic acid vitamin that is important for development of the nervous system, 493
Follicle-stimulating hormone (FSH) chemical released from the anterior pituitary; promotes the growth of a follicle in the ovary, *59*, 332, 333, *333*
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Footbridge dilemma, 359
Forebrain most anterior part of the brain; consists of two cerebral hemispheres, *71*, *72*, 73–77, 118
Fovea a tiny area of the retina specialized for acute, detailed vision, *149*, 150–152, *152*, 162
Frequency the number of cycles per second, measured in Hz, 188
Frequency theory concept that the basilar membrane vibrates in synchrony with a sound, causing auditory nerve axons to produce action potentials at the same frequency, 189

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- Frontal cortex, *83*, *85*, 85–86
- **Frontal lobe** section of cerebral cortex that extends from the central sulcus to the anterior limit of the brain, *73–75*, *83*, 85–87
- **Frontotemporal dementia** intellectual deficit caused by gradual deterioration of the frontal and temporal cortices, 456
- FSH. *See* **Follicle-stimulating hormone**
- **Functional explanation** understanding why a structure or behavior evolved as it did, 6, *7*, 111
- **Functional magnetic resonance imaging (fMRI)** a modified version of MRI that measures energies based on hemoglobin instead of water; determines the brain areas receiving the greatest supply of blood and using the most oxygen, *94*, 94–95, 97, *98*
- Fungiform papilla, 212, 214, *215*
- **Fusiform gyrus** brain area of the inferior temporal cortex that recognizes faces, *178*, 178–180

- *g* hypothetical ability responsible for the tendency of all cognitive test scores to correlate positively with one another, 417
- GABA (gamma-aminobutyric acid), 50, 52, 53, 273, 275
- **GABA$_A$ receptor** receptor complex structure that includes a site that binds GABA as well as sites that modify the sensitivity of the GABA site, 372–373, 412
- Gambling, 464
- Gambling Task, 454, 455
- **Ganglion cells** type of neuron in the retina that receives input from the bipolar cells, 150, *151*, *152*, 153, *161*, 164
- Ganglion/Ganglia, 68, *68*
- **Gap junction** a direct contact of one neuron with another, enabling electrical transmission, 56, *57*
- **Gases** one of the categories of neurotransmitters, including nitric oxide and possibly others, 50, *50*
- **Gate theory** idea that stimulation of certain axons can close the “gates” for pain messages, 206
- Gender differences, 339
- **Gender identity** the gender that a person considers himself or herself to be, 339–342
- **General adaptation syndrome** a generalized response to stress, 376–377
- **Genes** units of heredity that maintain their structural identity from one generation to another, 104–107, *106*, 109–110
  - activity of, 108
  - candidate gene approach, 109
  - gene-knockout approach, 92, *98*
  - homeobox, 117
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  - and sexual orientation, 342–345, *343*
  - and violence, 364, *364*
- Genitals, *326*, 327–329
- **Ghrelin** chemical released by the stomach during a period of food deprivation; also released as a neurotransmitter in the brain, where it stimulates eating, *311*, 312
- *Ginkgo biloba,* 414
- **Glia** type of cell in the nervous system that, in contrast to neurons, does not conduct impulses over long distances, 5, *5*, 18–19, *20*
- **Globus pallidus** large subcortical structure; part of the basal ganglia, 75, *76*, *242*, 242–243
- **Glucagon** pancreatic hormone that stimulates the liver to convert stored glycogen to glucose, *58*, *309*, 309–310
- **Glucose** a simple sugar, 21, *309*, 309–310
- Glutamate, 52, 124, 136–137, 203, 412, 488–489
- **Glutamate hypothesis of schizophrenia** proposal that schizophrenia relates in part to deficient activity at glutamate synapses, especially in the prefrontal cortex, 488–489
- **Golgi tendon organs** receptors that respond to increases in muscle tension; inhibit further contractions, 229, *229*
- Goose bumps, 111–112, 294
- **G protein** a protein coupled to guanosine triphosphate (GTP), an energy-storing molecule, 53, *53*
- **Graded potential** a membrane potential that varies in magnitude in proportion to the intensity of the stimulus, 33
- Grasp reflex, 112, *112*
- **Gray matter** areas of the nervous system that are densely packed with cell bodies and dendrites, *68*, 69, *69*
- **Grid cells** entorhinal cortex cells that respond when an animal is in any of a number of places arranged in a hexagonal grid pattern, 401
- **Group selection** evolutionary selection favoring a gene because of its benefits to a group, 113
- Guanine, 105
- *Gymnema sylvestre,* 213
- Gyrus, *68*, *73*, *128*

- **Habituation** a decrease in response to a stimulus that is presented repeatedly and accompanied by no change in other stimuli, 410, *410*
- **Hair cells** the auditory receptors that lie along the basilar membrane in the cochlea, 189, *190*
- Hair-follicle receptors, *199*
- **Hallucinations** false sensory experiences, 84, 475
- **Hallucinogenic drugs** drugs that distort perception, 54, 475
- Hamilton Depression Rating Scale, 474
- **Hard problem** philosophical question as to why and how brain activity is conscious, 442, 443
- Head injuries. *See* Brain damage
- Hearing aids, 195, 437
- Hearing deficits, and schizophrenia, 483, 485
- Hearing loss, 195
- **Hebbian synapse** a synapse that increases in effectiveness because of simultaneous activity in the presynaptic and postsynaptic neurons, 408–409
- Hemiplegia, *238*
- **Hemorrhage** type of stroke resulting from a ruptured artery, 136
- **Heritability** estimate of the degree to which variation in a characteristic depends on genetic variations in a given population, 108–110
- Heroin, 54, 464–465, 467
- **Heterozygous** having two unlike genes for a given trait, 105, *106*
- Hibernation, 281–282, 292
- **Hindbrain** the posterior part of the brain, *71*, 71–73, *118*, 118–119
- **Hippocampus** a large structure located toward the posterior of the forebrain, between the thalamus and the cerebral cortex, *74*, 75–77, 395–400
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  - as part of the limbic system, 355
  - and schizophrenia, 484–485
  - and stress, 378–379
- Histamine, 274
- **Histones** proteins that bind DNA into a shape that resembles a string wound around a ball, 107
- Hold function, 240
- Homeobox genes, 117

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Huntington’s disease neurological disorder characterized by jerky arm movements and facial twitches and later by tremors, writhing movements, and psychological symptoms, 251–253, *252*, *253*, 483
5-hydroxyindoleacetic acid (5-HIAA) serotonin’s main metabolite, 365, *365*
Hypercomplex cells visual cortex cells that respond to a bar-shaped pattern of light in a particular orientation, but only if it does not extend beyond a certain point, 166, *167*
Hyperpolarization increased polarization across a membrane, 28
Hypocretin neurotransmitter that increases wakefulness and arousal, 274
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Impotence the inability to have an erection, 332
Inattentional blindness tendency to ignore most changes in a scene that occur slowly or during an eyeblink, 447
Infant amnesia tendency to forget the experiences of early childhood, 392
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Inferior colliculus swelling on the surface of the tectum that contributes to hearing, 71, *73*
Inferior temporal cortex portion of the cortex where neurons are highly sensitive to complex aspects of the shape of visual stimuli within very large receptive fields, *176*, 177–178
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Inhibitory postsynaptic potential (IPSP) temporary hyperpolarization of a membrane, 42
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Inner-ear deafness hearing loss that results from damage to the cochlea, the hair cells, or the auditory nerve, 195
Insomnia inadequate sleep, 276
Instrumental conditioning a type of condition in which reinforcement or punishment changes the future probabilities of a given behavior, 384–386, *385*
Insulin pancreatic hormone that enables glucose to enter the cells, 50, *58*, 309–310, *310*, *311*
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Interpreter tendency of the left hemisphere to invent an explanation for an action when the true cause was unconscious, 429
Intersex a person whose sexual development is intermediate or ambiguous, 339–340, *340*
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Intrinsic neuron neuron whose axons and dendrites are all confined within a given structure, 17, *41*
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Koniocellular neurons small ganglion cells that occur throughout the retina, 165, *165*
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Lateral geniculate nucleus thalamic nucleus that receives incoming visual information, 161, *162*, 165
Lateral hypothalamus area of the hypothalamus that controls insulin secretion, alters taste responsiveness, and facilitates feeding in other ways, 312–313, *313, 314*
Lateral inhibition the reduction of activity in one neurons by activity in neighboring neurons, 163, *163*
Lateral interpositus nucleus (LIP) a nucleus of the cerebellum that is essential for certain conditioned responses, 387, *388*
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Locus coeruleus a small structure in the pons that emits bursts of impulses in response to meaningful events, especially those that produce emotional arousal, *273, 274*
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Long-term memory memory of events that occurred further back in time, 388–389, 395–397
Long-term potentiation (LTP) phenomenon that when one or more axons connected to a dendrite bombard it with a rapid series of stimuli, some of the synapses become more responsive to new input of the same type for minutes, days, or weeks, 410–413, *413*
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LSD (lysergic acid diethylamide), 54, *57*
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LTP. *See* **Long-term potentiation**
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Luteinizing hormone (LH) hormone released from the anterior pituitary that causes the follicle to release an ovum, *58*, 332

Magnetic resonance imaging (MRI) method of imaging a living brain by using a magnetic field and a radio frequency field to make atoms with odd atomic weights all rotate in the same direction and then removing those fields and measuring the energy that the atoms release, 96, *97*, *98*, 137
Magnetoencephalograph (MEG) a device that measures the faint magnetic fields generated by brain activity, 93, *94*, *98*
Magnocellular neurons large cell bodies with large receptive fields that are distributed evenly throughout the retina, 165, *165*
Major depression a condition in which people feel sad and helpless every day for weeks at a time, *470*, 470–472. *See also* **Antidepressant drugs**
Mania a condition characterized by restless activity, excitement, laughter, selfconfidence, rambling speech, and loss of inhibitions, 477
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Medial corticospinal tract set of axons from many parts of the cerebral cortex, midbrain, and medulla; responsible for control of bilateral muscles of the neck, shoulders, and trunk, *238*, 239
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- MEG. *See* **Magnetoencephalograph**
- Meissner's corpuscles, *199*, *200*
- **Melanocortin** type of chemical that promotes satiety, 311, 312
- **Melatonin** hormone that influences both circadian and circannual rhythms, *58*, *266*, 306–307
- **Membrane** structure that separates the inside of the cell from the outside environment, 15, *15*, *26*, 27–31
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  - and schizophrenia, 481
  - sex hormones, 331–332
- Mendelian genetics, 104–108
- **Meninges** membranes that surround the brain and spinal cord, 77
- **Menstrual cycle** a periodic variation in hormones and fertility over the course of about 28 days, 332–334, *333*
- **Mentalism** view that only the mind really exists and that the physical world could not exist unless some mind were aware of it, 442
- Merkel disks, 200, *200*
- Mesostriatal system, 487, *488*
- **Metabotropic effects** a sequence of metabolic reactions that produce slow and longlasting effects at a synapse, 52–54, *54*
- **Methadone** drug similar to heroin and morphine that is taken orally, 54, 467
- Methods. *See* Research methods
- **Methylphenidate** stimulant drug prescribed for ADHD that increases the stimulation of dopamine synapses by blocking the reuptake of dopamine by the presynaptic neuron, 55, *57*, 414
- **Microdeletion** deletion of a small part of a chromosome, 484
- Microelectrodes, 26, 28, 41, 42
- **Microglia** cells that remove waste material and other microorganisms from the nervous system, 18, *20*
- **Midbrain** middle part of the brain, *71*, 73, *73*, *81*, 118
- Middle ear, 189, 195
- **Middle-ear deafness** hearing loss that occurs if the bones of the middle ear fail to transmit sound waves properly to the cochlea, 195
- Middle temporal cortex, 180–181
- Middle temporal cortex (area MT), 180–181, *181*
- **Midget ganglion cells** ganglion cells in the fovea of humans and other primates, 150
- **Migrate** movement of brain neurons or glia, 118
- **Mind-body problem** or **mind-brain problem** question about the relationship between mental experience and brain activity, 4, 441
- **Minimally conscious state** condition of decreased brain activity with occasional, brief periods of purposeful actions and limited speech comprehension, 269
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- **Mirror neurons** cells that are active during a movement and while watching someone else perform the same movement, 237
- **Mitochondrion** structure that performs metabolic activities, 15
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- **Monism** belief that the universe consists of only one kind of substance, 441–442
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- **Monoamine oxidase inhibitors (MAOIs)** drugs that block the enzyme monoamine oxidase (MAO), a presynaptic terminal enzyme that metabolizes catecholamines and serotonin into inactive forms, 473, *473*
- **Monoamines** chemicals formed by a change in certain amino acids, *50*
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- **Morris water maze** a procedure used to test for spatial memory in nonhumans, 400, *400*
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- **Motor program** a fixed sequence of movements, 231
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- **MPTP** a chemical that the body converts to MPP$^+$, 250
- MRI. *See* **Magnetic resonance imaging**
- **MST** (medial superior temporal cortex), temporal cortex area that responds best to the expansion, contraction, or rotation of a visual display, 180–183, *182*
- **MT** (or **V5**) area of the middle temporal lobe that is important for perception of visual motion, *176*, 180–181, *181*
- **Mullerian ducts** embryonic structures that can develop into a female's oviducts, uterus, and upper vagina, 326, *326*
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Nucleus accumbens brain area that is rich in dopamine and is central to the brain's reinforcement system, *314*, 334, *463*, 463–464, 470
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Osmotic pressure tendency of water to flow across a semipermeable membrane from the area of low solute concentration to the area of high solute concentration, 300, *301*
Osmotic thirst thirst triggered by certain neurons that detect the loss of their own water, 300–302, *301*
Oval window a membrane of the inner ear, 189, *190*
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Periovulatory period time around the middle of the menstrual cycle of maximum fertility and high estrogen levels, 334
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PGO waves a distinctive pattern of highamplitude electrical potentials that occur first in the pons, then in the lateral geniculate, and then in the occipital cortex, *274*, 274–275
Phantom limb a continuing sensation of an amputated body part, 139–141, *141*
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Phase-delay, 261, 265, 276, *477*
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Phencyclidine (PCP) drug that inhibits the NMDA glutamate receptors, 488
Phenothiazines a chemical family that includes antipsychotic drugs (chlorpromazine) that relieve the positive symptoms of schizophrenia, 486
Phenylketonuria (PKU) a genetic inability to metabolize the amino acid phenylalanine, 109
Phenylthiocarbamide (PTC), 105
Pheromones chemicals released by an animal that affect the behavior of other members of the same species, 292
Phi phenomenon tendency to see something as moving back and forth between positions when in fact it is alternately blinking on and off in those positions, 446
Photopigments chemicals contained in rods and cones that release energy when struck by light, 153
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Pineal gland an endocrine gland located just posterior to the thalamus that releases the hormone melatonin, *57*, *71*, *264*, 266
Pinna the outer ear structure of flesh and cartilage that sticks out from each side of the head, 189, *190*
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Pitch the aspect of auditory perception related to the frequency of a sound, 188, 189–191, 195
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Place cells hippocampal neurons that respond most strongly when an animal

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Pontomesencephalon part of the reticular formation that contributes to cortical arousal, 273, *273*
Positive symptoms presence of behaviors not seen in normal people, 482
Positron-emission tomography (PET) method of mapping activity in a living brain by recording the emission of radioactivity from injected chemicals, 93–94, *94*, *98*
Postcentral gyrus area just posterior to the central gyrus; primary receptor site for touch and other body sensations, *83*, 83–84, *84*
Posterior, *67*, *68*
Posterior parietal cortex area with a mixture of visual, somatosensory, and movement functions, particularly in monitoring the position of the body relative to objects in the world, *234*, 235–236
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Purines a category of chemicals including adenosine and several of its derivatives, *50*

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Sex-linked gene gene on either the X or the Y chromosome, 106–107, *107*
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Slow-wave sleep (SWS) sleep occupied by slow, large-amplitude brain waves, 270, *270*, 271
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Sodium-potassium pump mechanism that actively transports sodium ions out of the cell while drawing in two potassium ions, 26, 27, *27*, 136, 307
Sodium-specific hunger increased preference for salty tastes, 302
Soma (cell body) structure containing the nucleus, ribosomes, and mitochondria, 16, *17*
Somatic nervous system part of the PNS that consists of the axons conveying messages from the sense organs to the CNS and from the CNS to the muscles, 67
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Spatial neglect a tendency to ignore the left side of the body or the left side of objects, 449
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Spatial summation combination of effects of activity from two or more synapses onto a single neuron, 42
Special experiences, effects of, 127–131
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Specificity property that highly active synapses become strengthened and less active synapses do not, 411

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- **Spinal cord** part of the CNS; it communicates with all the sense organs and muscles except those of the head, *17*, *19*, 68–69, *69*, *201*
  - cross-section of, *67*, *68*
  - damage/disorders, 233, *238*
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  - in ventral surface, 73
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- Split-brain operation, 427–430
  - competition and cooperation, 428–429
  - right hemisphere, 429–430
- **Split-brain people** people who have undergone surgery to the corpus callosum, 427
- **Spontaneous firing rate** a periodic production of action potentials even without synaptic input, 43
- **SRY** the sex-determining region on the Y chromosome, 326
- SSRIs. *See* **Selective serotonin reuptake inhibitors (SSRIs)**
- **Startle reflex** response that one makes after a sudden, unexpected loud noise or similar sudden stimulus, 366–367
- **Stem cells** undifferentiated cells that divide and produce daughter cells that develop more specialized properties, 118, 251
- **Stereotaxic instrument** a device for the precise placement of electrodes in the brain, 91, *91*
- **Steroid hormones** hormones that contain four carbon rings, 327, *327*
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  - masking, 443–444
  - timing of consciousness, 446
  - unattended stimulus, 445
- St. John's wort, 473
- Stomach, in regulation of feeding, 308
- **Strabismus** (or strabismic amblyopia or lazy eye) a condition in which the eyes do not point in the same direction, 170, *170*
- **Stress** the nonspecific response of the body to any demand made upon it; also defined as events that are interpreted as threatening, 376–379
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  - and depression, 470–471, *471*
  - and gene activity, 108
  - general adaptation syndrome, 376–377
  - and HPA axis, 376
  - immune system, 377–378
- **Stretch reflex** a reflexive contraction of a muscle in response to a stretch of that muscle, 229
- Striate cortex, 83, 165
- **Striated muscles** muscles that control movement of the body in relation to the environment, 226
- **Striatum** forebrain structure composed of the caudate nucleus and putamen, which are important for certain aspects of movement and learning, 242, *243*, 244, 402–403, *403*
- **Stroke** a temporary loss of normal blood flow to a brain area, 136–138, *137*
- **Stroop effect** the difficulty of saying the color of ink of a word instead of reading the word itself, 448
- Structure of vertebrate nervous system, 66–78
  - autonomic nervous system, 69–70
  - forebrain, *71–72*, 73–77
  - hindbrain, 71–73
  - midbrain, *72*, 73
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- **Subfornical organ (SFO)** brain structure adjoining the third ventricle of the brain, where its cells monitor osmotic pressure and sodium concentration, 301, *301*
- Substance abuse, 461–467, 483
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  - drug mechanisms, 462–465
  - predispositions, 465–466
  - and schizophrenia, 481–482
  - tolerance and withdrawal, 464–465
  - treatments, 466–467
- **Substance-induced psychotic disorder** condition similar to schizophrenia, provoked by large, repeated doses of a drug, 487
- **Substantia nigra** a midbrain structure that gives rise to a pathway releasing dopamine, 73, 242, *242–243*, *249*, 250
- Subthreshold stimulation, 28
- Sulcus, 234
- Superior, *68*
- **Superior colliculus** swelling on either side of the tectum; important to visual processing, 71, *71*, 73
- **Supertasters** people with a higher than average number of taste buds, 214–215, *215*
- **Supplementary motor cortex** area of the frontal cortex; active during preparation of a rapid sequence of movements, *234*, 236
- **Suprachiasmatic nucleus (SCN)** part of the hypothalamus; provides the main control of the circadian rhythms, 263, *264*
- **Supraoptic nucleus** part of the hypothalamus that controls the release rate of vasopressin, 301
- SWS. *See* **Slow-wave sleep**
- **Sympathetic nervous system** a network of nerves that prepare the organs for vigorous activity, *68*, 69, *70*, 352–353, *353*
- **Synapse** a specialized gap as a point of communication between two neurons anatomy of chemical events, 40–45, *51*
  - chemical events at, *48*, 48–59, *49*
  - competition among axons, 122
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  - inhibitory, 42–44, *43*, 163–165
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  - relationship between EPSP, IPSP, and action potentials, 44–45
  - wiring diagram for, *45*
- **Synaptic cleft** the space between the presynaptic and postsynaptic neurons, 49
- Synaptic delay, *41*
- **Synaptogenesis** formation of synapses, 118–119
- Syndromal obesity, 315
- **Synesthesia** the experience some people have in which stimulation of one sense evokes a perception of that sense and another one also, 220

- Tabes dorsalis, *238*
- Tangles, *391*, 392
- **Tardive dyskinesia** a movement disorder characterized by tremors and other involuntary movements, 487–488
- Taste, 105, 211–216, *212*, *213*
- **Taste buds** receptors on the tongue that detect certain chemicals, 211, *212*
- Taste coding in brain, 214
- Taste receptors, 211, 214
- Taste sensitivity, 214–216
- **Tau protein** part of the intracellular support structure of axons, 390
- T cells, 377, *378*
- **Tectum** roof of the midbrain, *71*, 73
- **Tegmentum** intermediate level of the midbrain, 73
- Telencephalon, *71*
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  - body temperature control, 262
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  - homeostasis and allostasis, 293–294
- Temporal cortex, *83*, 87, 180–181
- **Temporal lobe** the lateral portion of each hemisphere, near the temples, *75*, *83*, 84–85
- **Temporal summation** a cumulative effect of repeated stimuli within a brief time, 41–42, *43*
- **Testes** sperm-producing organs, 326
- **Testicular feminization** condition in which individuals with an XY chromosome

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Thalamus a pair of structures in the center of the forebrain, 74, *74*, 75, *76*, *314*
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  in sagittal section of the brain, *73*
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  in the visual system, 161–162
Thiamine a B1 vitamin necessary to use glucose, 22
Thirst, 300–302
Threshold of excitation minimum amount of membrane depolarization necessary to trigger an action potential, 28
Thymine, 105
Thyroid hormones, 59, *59*
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Timbre tone quality or complexity, dependent on the harmonics of the tone, 189
Time cells hippocampal neurons that respond most strongly at a particular point within a sequence of times, 401
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Tinnitus frequent or constant ringing in the ears, 195
Tissue plasminogen activator (tPA) drug that breaks up blood clots, 136–137
TMS. *See* **Transcranial magnetic stimulation**
Tolerance decreased effect of a drug after repeated use, 464–465
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tPA. *See* **Tissue plasminogen activator**
Tract, *68*
Transcranial magnetic stimulation (TMS) the application of an intense magnetic field to a portion of the scalp, temporarily inactivating neurons below the magnet, 92, *92*, *98*
Transgender person who strongly identifies with the gender other than the one assigned at birth, 345–346
Transmitter-gated channel ion channel that opens temporarily when a neurotransmitter binds to it, 52
Transporter special membrane protein where reuptake occurs in the neurotransmitter binds to it, 54
Trichromatic theory (Young-Helmholtz theory) theory that color is perceived through the relative rates of response by three kinds of cones, each one maximally sensitive to a different set of wavelengths, 154–155
Tricyclics antidepressant drugs that block the reuptake of catecholamines and serotonin by presynaptic terminals, 472
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Type 2 impaired glucose absorption caused by cells' decreased response to insulin, 310

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Unconditioned stimulus (UCS) stimulus that automatically evokes an unconditioned response, 384, *385*
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V5. *See* **MT**
Vagus nerve tenth cranial nerve, which has branches to and from stomach and several other organs, 308
Vas deferens, 326, *326*
Vasopressin (antidiuretic hormone) hormone released by posterior pituitary; raises blood pressure and enables kidneys to conserve water, 59, *59*, 300, 301, 335, *335*
Vegetative state condition in which someone has decreased brain activity and alternates between wakefulness and sleep but shows only limited responsiveness, such as increased heart rate in response to a painful stimulus, 269
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Ventral posterior nucleus, *76*
Ventral stream visual paths in the temporal cortex that are specialized for identifying and recognizing objects; the "what" path, 176–177
Ventral toward the stomach, 67, *67*, *68*
Ventricles four fluid-filled cavities within the brain, *73*, *74*, 77–78
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Ventromedial hypothalamus (VMH) region of the hypothalamus in which damage leads to faster stomach emptying and increase secretion of insulin, 313, *313–315*, 315, 330
Ventromedial prefrontal cortex brain area that updates preferences based on recent information and monitors confidence in a decision, 360, 454, *454*, 456
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Voltage-gated channels membrane channel whose permeability to sodium (or some other ion) depends on the volt difference across the membrane, 29

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